IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff, v. IMPAX LABORATORIES, INC., Defendant.	Civil Action No.: 06-222 JJF **PUBLIC VERSION**

DECLARATION OF MARY B. MATTERER
IN SUPPORT OF DEFENDANT'S MOTION TO
COMPEL A RESPONSE TO INTERROGATORY NO. 35

RICHARD K. HERRMANN (No. 405)
MARY B. MATTERER (I.D. No. 2696)
MORRIS JAMES LLP
500 Delaware Ave., 15th Floor
Wilmington, DE 19801
Telephone: (302) 888-6800
mmatterer@morrisjames.com

M. PATRICIA THAYER (*pro hac vice*)
JOHN M. BENASSI (*pro hac vice*)
JESSICA R. WOLFF (*pro hac vice*)
DANIEL N. KASSABIAN (*pro hac vice*)
SAMUEL F. ERNST (*pro hac vice*)
HELLER EHRMAN LLP
4350 La Jolla Village Drive, 7th Floor
San Diego, CA 92101
Telephone: (858) 450-8400
Facsimile: (858) 450-8499

Attorneys for Defendant
IMPAX LABORATORIES, INC.

Original Date: February 6, 2007
Redacted Version: February 13, 2007

I, Mary B. Matterer, declare:

1. I am a partner at the law firm of Morris James LLP, counsel to Defendant Impax Laboratories, Inc. ("Impax") in this matter.

2. Attached hereto as Exhibit 1 is a copy of a Complaint filed July 26, 2006 in Civil Action No. 9:06CV156, pending in the United States District Court, Eastern District of Texas, *Alza Corporation v. Wyeth et al.*.

3. Attached hereto as Exhibit 2 is a document purporting to be internal correspondence of Plaintiff Wyeth ("Wyeth), produced by Wyeth in this litigation and bearing Bates Nos. WYETH 012-00150 – 012-00165.

4. Attached hereto as Exhibit 3 is a document purporting to be the Final Report from Clinical Study 600B-134-US, produced by Wyeth in this litigation and bearing Bates Nos. WYETH 022-001711 – 022-001799.

5. Attached hereto as Exhibit 4 is Impax's Second Set of Interrogatories (Nos. 20-40 to Wyeth), served on September 8, 2006.

6. Attached hereto as Exhibit 5 is Alza's Patent Cooperation Treaty Application No. WO 94/27589.

7. Attached hereto as Exhibit 6 is Wyeth's Responses to Impax's Second Set of Interrogatories (Nos. 20-40), served on October 10, 2006.

8. Attached hereto as Exhibit 7 is a copy of an October 30, 2006 letter from Samuel F. Ernst, counsel to Impax, to Linda A Wadler, counsel to Wyeth.

9. Attached hereto as Exhibit 8 is a copy of a November 27, 2006 letter from Samuel F. Ernst counsel to Impax, to Linda A. Wadler, counsel to Wyeth.

10. Attached hereto as Exhibit 9 is a copy of a December 4, 2006 letter from Barbara R. Rudolph, counsel to Wyeth, to Samuel F. Ernst, counsel to Impax.

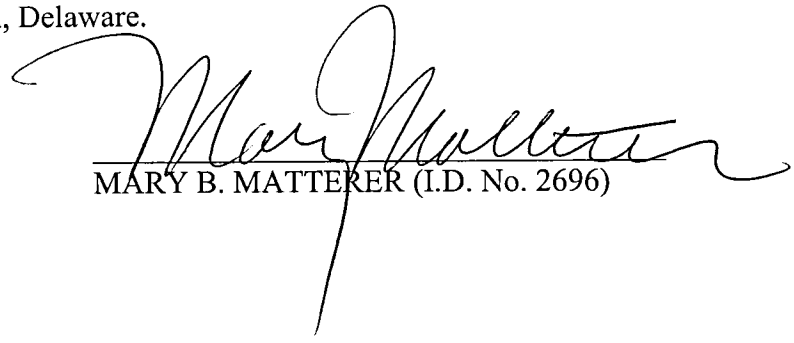
11. Attached hereto as Exhibit 10 is a copy of a January 29, 2007 letter from Samuel F. Ernst, counsel to Impax, to Robert A. Pollock, counsel to Wyeth.

12. Attached hereto as Exhibit 11 is a copy of a February 2, 2007 letter from Robert A. Pollock, counsel to Wyeth, to Samuel F. Ernst, counsel to Impax.

13. Attached hereto as Exhibit 12 is a copy of a February 5, 2007 letter from Samuel F. Ernst, counsel to Impax, to Robert A. Pollock, counsel to Wyeth.

14. Attached hereto as Exhibit 13 is a copy of a February 5, 2007 letter from Barbara R. Rudolph, counsel to Wyeth, to Daniel N. Kassabian, counsel to Impax.

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct and that this declaration was executed on this sixth day of February, 2007 at Wilmington, Delaware.



MARY B. MATTERER (I.D. No. 2696)

EXHIBIT 1

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF TEXAS
LUFKIN DIVISION

ALZA CORPORATION, a Delaware corporation,

Plaintiff,

v.

WYETH, a Delaware corporation, and WYETH PHARMACEUTICALS, INC., a Delaware corporation,

Defendants.

C.A. No. 9:06cv156

JURY TRIAL DEMANDED

COMPLAINT

Plaintiff Alza Corporation ("Alza"), by its undersigned counsel, brings this action for patent infringement against defendants Wyeth and Wyeth Pharmaceuticals, Inc. (collectively "Defendants") and alleges as follows:

Jurisdiction and Venue

1. This action is based upon the Patent Laws of the United States, Title 35 of the United States Code, for infringement of United States Patent No. 6,440,457 ("the '457 Patent").

2. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

3. Venue properly lies in this judicial district under 28 U.S.C. §§ 1391 and 1400(b).

4. This Court has personal jurisdiction over Defendants.

Parties

5. Alza is a Delaware corporation with a principal place of business at 1900 Charleston Road, Mountain View, California 94039.

6. On information and belief, Wyeth is a Delaware corporation with a principal place of business at Five (5) Giraldo Farms, Madison, New Jersey 07940.

7. On information and belief, Wyeth Pharmaceuticals, Inc., is a Delaware corporation with a place of business at 500 Arcola Road, Collegeville, Pennsylvania 19426.

8. On information and belief, Wyeth Pharmaceuticals, Inc., is a subsidiary of Wyeth.

9. On information and belief, at least in part for its own benefit, Wyeth directed, authorized, assisted, cooperated with, or participated in the acts of Wyeth Pharmaceuticals, Inc., about which Alza complains.

Claim of Patent Infringement

10. Alza realleges paragraphs 1 through 9 above as if fully set forth herein.

11. On August 27, 2002, the '457 Patent, entitled "Method of Administering Antidepressant Dosage Form," was duly and legally issued by the United States Patent and Trademark Office to Alza as the assignee of the inventors, David Emil Edgren, Gurdish Kaur Bhatti, Zahedeh Hatamkhani, and Patrick S. L. Wong. The '457 Patent remains in full force and effect and will expire no earlier than August 27, 2019. A true and correct copy of the '457 Patent is attached to this Complaint as Exhibit A.

12. Alza has been and remains the owner of all right, title, and interest in and to the '457 Patent.

13. On information and belief, Defendants contributorily infringe and induce infringement of Claim 1 of the '457 Patent under 35 U.S.C. § 271, including but not limited to

§§ 271(b)-(c) and (f). Defendants contributorily infringe and induce infringement of the '457 Patent through various activities including but not limited to the manufacture, use, sale, and offer for sale of Effexor® XR products in the United States after the '457 Patent issued.

14. On information and belief, Defendants knew of the '457 Patent at all relevant times before making, using, selling, or offering for sale Effexor® XR products.

15. On information and belief, Defendants have in the past offered for sale and sold, and continue to offer for sale and sell Effexor® XR products that constitute a material part of the invention claimed in the '457 Patent and that have no substantial use other than as an infringement of the '457 Patent.

16. On information and belief, Defendants knew and intended that purchasers of Effexor® XR products would use the products in methods so as to infringe the '457 Patent.

17. On information and belief, Defendants have actively induced purchasers of Effexor® XR products to use the products in methods so as to infringe the '457 Patent.

18. On information and belief, purchasers of Effexor® XR products use the products in methods so as to infringe the '457 Patent.

19. On information and belief, Defendants have in the past willfully infringed, and continue to willfully infringe, the '457 Patent through their manufacture, use, sale, and offer for sale of Effexor® XR products.

Prayer For Relief

WHEREFORE, Alza prays for a judgment against Defendants as follows:

(a) adjudging that Defendants have infringed the '457 Patent under 35 U.S.C. § 271;

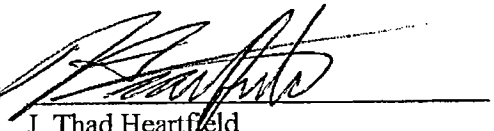
(b) ordering Defendants to account for and pay to Alza all damages caused to Alza by reason of Defendants' infringement of the '457 Patent, together with prejudgment interest on all damages;

(c) increasing the damages three times based on the willful nature of Defendants' infringement under 35 U.S.C. § 284;

(d) granting Alza its reasonable attorney fees under 35 U.S.C. § 285; and

(e) for such further and additional relief as this Court deems just and proper.

Date: July 26, 2006

By: 

J. Thad Heartfield
Texas Bar No. 09346800
LAW OFFICES OF
J. THAD HEARTFIELD
2195 Dowlen Rd.
Beaumont, TX 77706
Telephone: (409) 866-3318
Fax: (409) 866-5789
E-mail: thad@jth-law.com

Attorneys for Plaintiff Alza Corporation

Exhibit A

U.S. Patent No. 6,440,457

US006440457B1

(12) **United States Patent**
Edgren et al.

(10) **Patent No.: US 6,440,457 B1**
(45) **Date of Patent: Aug. 27, 2002**

(54) **METHOD OF ADMINISTERING ANTIDEPRESSANT DOSAGE FORM**

(75) Inventors: **David Emil Edgren**, El Granada; **Gurdish Kaur Bhatti**; **Zahedeh Hatamkhani**, both of Fremont; **Patrick S. L. Wong**, Palo Alto, all of CA (US)

(73) Assignee: **Alza Corporation**, Mountain View, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/068,480**

(22) Filed: **May 27, 1993**

(51) **Int. Cl.**[7] **A61K 9/22**; A61K 9/52; A61K 31/137; A61P 25/24

(52) **U.S. Cl.** **424/468**; 424/457; 424/473; 514/964; 514/654

(58) **Field of Search** 424/473, 468, 424/457; 514/964, 654

(56) **References Cited**

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Primary Examiner—Edward J. Webman
(74) *Attorney, Agent, or Firm*—Robert R. Neller

(57) **ABSTRACT**

The invention pertains to a dosage form **10** and to administering an antidepressant medicament **16** for an extended period of time in a rate-known dose.

1 Claim, 1 Drawing Sheet

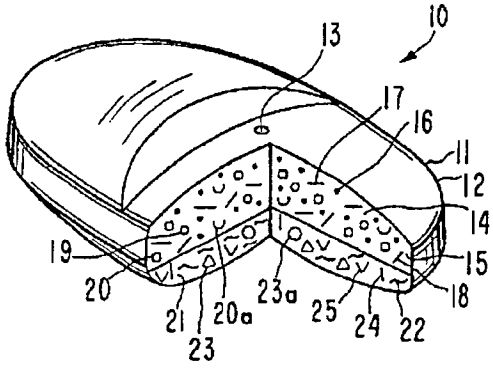


FIG.1

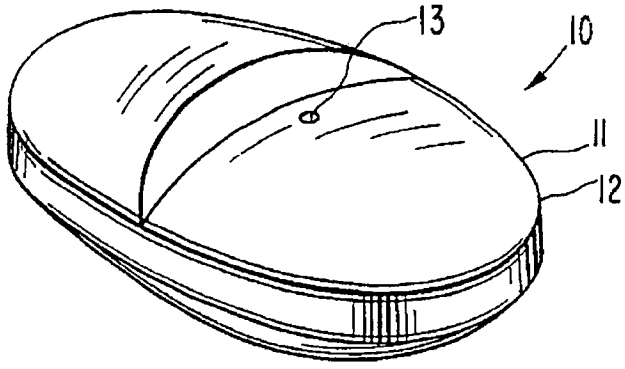


FIG.2

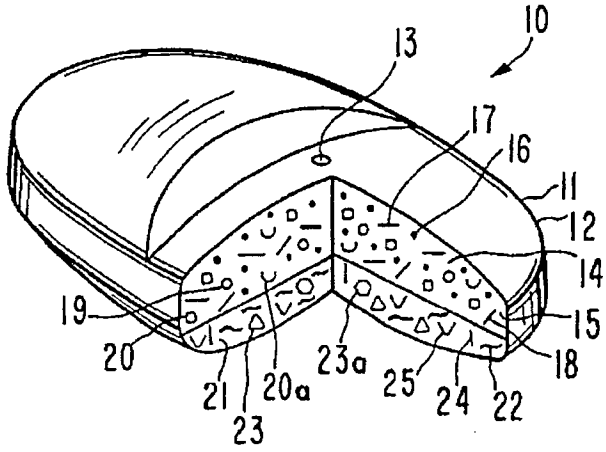
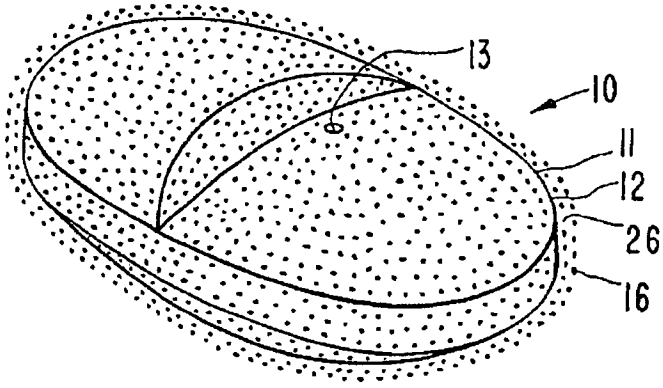


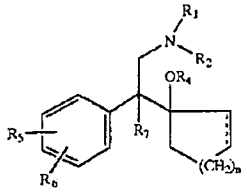
FIG.3



METHOD OF ADMINISTERING ANTIDEPRESSANT DOSAGE FORM

FIELD OF THE INVENTION

This invention pertains to a controlled-release dosage form comprising a compound of the following structural formula:



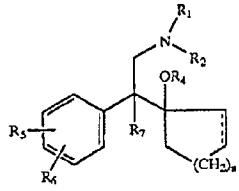
useful for antidepressant therapy. The invention concerns also a method useful for antidepressant therapy by administering the controlled-release dosage form comprising the compound of the formula.

BACKGROUND OF THE INVENTION

The primary goal of drug administration is to provide a therapeutic dose of drug in the body to achieve a desired blood concentration, and then maintain the desired drug blood concentration. The prior art, in attempts to obtain the desired therapeutic effect, often used different dosage forms or programs. One dosage program consists of a single dosing of the drug from a conventional capsule or tablet that produced a rapid rise followed by an immediate decline of the drug blood level versus time. The single dosing does not maintain the drug within a therapeutic range for an extended period of time, but exhibits of a short duration of action due to the inability of the conventional dosage form to provide drug delivery over time.

Another prior art dosing program used to obtain and to achieve drug blood levels consists in administering the drug repetitively using conventional dosage forms at various dosing intervals, as in multiple-dose therapy. In administering a drug according to the multiple-dose therapy, the drug blood level reached and the time required to reach that level depends on the dose and the dosing interval. There are, however, several potential problems inherent in multiple dose therapy. For example, if the dosing interval is not appropriate for the biological half-life of the drug, large peaks and valleys may result in the drug blood levels. Also, the drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for many disease states. And too, patient noncompliance with the multiple dosing regimen can result in a failure of this approach, especially as a drug in circulation surges to a high each time the drug is administered followed by a decline in drug concentration in the blood and in body compartments. Thus, a graph of drug in circulation following a dosage program of several doses, has an appearance of a series of peaks:, which may surpass the toxic threshold. Then, each time the blood levels decreases into valleys, below a critical level needed to achieve a desired therapeutic effect, that effect may not be obtainable in the blood and body. Conventional dosage forms and their mode of operation are discussed in *Remington's Pharmaceutical Sciences,* 18th Edition, pages 1676 to 1686, (1990), Mack Publishing Co.; *The Pharmacological Basis of Therapeutics,* 7th Edition, page 7 (1985) published by MacMillian Publishing Co., and in U.S. Pat. Nos. 3,598,122 and 3,598,123 both issued to Zaffaroni.

A critical need exists for a controlled-rate dosage form for administering the drug of the formula:



which drug is presently administered in conventional dosage forms including tablets, capsules, elixirs and suspensions. These conventional dosage forms produce the peaks and valleys drug pattern presented above and they do not provide for controlled-rate therapy over an extended period of time. The drug of the formula is dosed twice or thrice a day now because of its elimination half-life of three to five hours. This pattern of dosing indicates the need for a controlled-release dosage form that can administer the drug at a controlled rate over an extended time to provide constant therapy and thereby eliminate the need for multiple dosing. The drugs of the structural formula are known in U.S. Pat. Nos. 4,535,186; 4,611,078; and 4,761,501 all issued to Husbands, Yardley and Muth.

The prior art provided controlled-release dosage forms that can continuously over time administer a drug for controlled-rate therapy. For example, in U.S. Pat. No. 4,327,725 issued to Cortese and Theeuwes and in U.S. Pat. Nos. 4,612,008; 4,765,989; and 4,783,337 issued to Wong, Barclay, Deters, and Theeuwes. The dosage forms disclosed in these patents provide a drug at a constant rate for effecting a therapeutic range for preferred therapy. The dosage forms of the patents provide a therapeutic range and avoids delivering the drug in excess in a toxic range with its accompanying side-effects. The dosage forms of the patents in providing a controlled dose in a therapeutic range also avoids delivering the drug in an ineffective dose in an ineffective range.

The dosage forms presented immediately above operate successfully for their intended use and they can deliver many drugs indicated for good therapy. The drugs of the above structural formula, however, possess properties such as a high solubility of 570 mg per ml at a body temperature of 37° C. that can lead to a premature release of the drug from the dosage form. During operation of the dosage forms, the convection motion of the imbibed fluid, and the hydrostatic pressure of the imbibed fluid coupled with the high solubility can result in the premature release of the drugs of the formula.

It is immediately apparent in the light of the above presentation that an urgent need exists for a dosage form endowed with controlled-release delivery for delivering the drugs embraced by the structural formula. The need exists for the dosage form for delivering the drug at a controlled dose in a therapeutic range while simultaneously providing the intended therapy. It will be appreciated by those versed in the dispensing art, that such a dosage form that can administer the drug in a controlled-rate dose over time, would, represent an advancement and a valuable contribution to the art.

OBJECTS OF THE INVENTION

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide a dosage from

that possesses controlled-release delivery for providing a dosage form for administering a drug of the structural formula.

Another object of the present invention is to provide a dosage form for administering the drug of the formula in a controlled-rate dose in a therapeutic range over a prolonged period of time.

Another object of the present invention is to provide a dosage form that can deliver the drug of the formula essentially-free of a premature release from the dosage form.

Another object of the present invention is to provide a drug delivery controlled-release system that can deliver a drug for maintaining constant drug levels in the blood thereby functioning as a prolonged release system.

Another object of the present invention is to provide drug delivery sustained-release system that provides slow release of the drug over an extended period of time optionally in a therapeutic range.

Another object of the present invention is to provide a dosage form that substantially reduces and/or substantially eliminates the unwanted influences of a gastrointestinal environment of use and still provides controlled drug administration.

Another object of the present invention is to provide an improvement in a dosage form for administering a drug embraced by the structural formula and its pharmaceutically acceptable salt, wherein the improvement comprises delivering the drug in a controlled-release rate from the dosage form for improved and known therapy.

Another object of the invention is to provide a once-a-day controlled-release dosage form to deliver the drug of the structural formula orally to a patent in need of therapy.

Another object of the invention is to provide a method for administering a drug of the formula by orally administering the drug in a controlled rate dose per unit dose over an extended time to an animal in need of therapy.

Another object of the present invention is to provide a method for administering a drug of the formula in a therapeutic range while simultaneously substantially-avoiding a toxic range and an infective range.

Another object of the present invention is to provide a therapeutic composition comprising a drug of the structural formula blended with a drug-composition forming polymer.

Another object of the invention is to provide a therapeutic composition comprising a member selected from the group consisting of venlafaxine and its pharmaceutically acceptable additional salt and a pharmaceutically acceptable polymer carrier for venlafaxine and its acceptable salts.

Other objects, feature, and advantages of the invention will more apparent to those versed in the dispensing arts from the following detailed specification, taken in conjunction with the drawings and the accompanying claims.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawing figures, which are not drawn to scale, but are set forth to illustrate various embodiments of the invention, the drawing figures are as follows:

Drawing FIG. 1 is a general view of a dosage form provided by the invention, which dosage form is designed and shaped for oral administration, and for a drug delivery in a controlled-rate dose in the gastrointestinal tract;

Drawing FIG. 2 is an opened view of the dosage form of drawing FIG. 1 for depicting the structure of the dosage form and the composition member contained inside the dosage form; and

Drawing FIG. 3 is a view of a dosage form that depicts an external, instant-release of drug of the structural formula coated on the exterior surface of the dosage form.

In the drawing figures, and in the specification, like parts in related figures are identified by like numbers. The terms appearing earlier in the specification and in the description of the drawing figures, as well as embodiments thereof, are further described elsewhere in the disclosure.

DETAILED DESCRIPTION OF THE DRAWINGS

Turning now to the drawing figures in detail, which drawing figures are examples of dosage forms provided by this invention, and which examples are not to be construed as limiting, one example of a dosage form is seen in drawing FIG. 1. In drawing FIG. 1, a dosage form **10** is seen comprising a body member **11**, which body **11** comprises wall **12**, that surrounds and forms an internal area, not seen in drawing FIG. 1. Dosage form **10** comprises at least one exit port **13** for connecting the exterior with the interior of dosage form **10**.

The dosage form **10** of drawing FIG. 1 illustrates a controlled-release dosage form manufactured as an osmotic dosage form that delivers a drug by osmotic action over an extended period of time. The dosage form comprising controlled-release properties embraced by this invention are successful at maintaining substantially constant drug levels in the blood or in a tissue. The dosage forms within the mode and manner of this invention comprises also sustained-release dosage forms. The sustained-release dosage forms releases the drug and provide drug levels in the blood or target tissue within a therapeutic range over an extended period of time. The invention embraces additionally prolonged release dosage forms. The prolonged release dosage form denotes extended duration of drug delivery action over that achieved by conventional drug delivery.

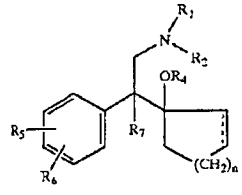
In drawing FIG. 2, dosage form **10** of FIG. 1 is seen in opened section. In drawing FIG. 2, dosage form **10** comprises a body **11**, a wall **12** that surrounds and defines an internal compartment **14**. In drawing FIG. 2, internal compartment **14** communicates through an exit passageway **13** with the exterior of dosage form **10**.

Wall **12** of dosage form **10** comprises totally or in at least a part of a composition that is permeable to the passage of an exterior fluid present in an environment of use, such as aqueous and biological fluids. Wall **12** is formed of nontoxic ingredients, is substantially impermeable to the passage of a drug and other ingredients present in compartment **14**. Wall **12** comprises a composition that is substantially inert, that is, wall **12** maintains its physical and chemical integrity during the drug dispensing life of a drug from dosage form **10**. The phrase, "maintaining its physical and chemical integrity," means wall **12** does not lose its structure and it does not change during the dispensing life of dosage form **10**, except for possible leaching of one or more exit **13** passageway formed during operation of dosage form **10** or for leaching a water-soluble flux enhancers blended into wall **12**. Wall **12** comprises a material that does not adversely affect an animal, a human or any other components comprising the dosage form. Representative materials for forming wall **12**, are in one embodiment, a cellulose ester polymer, a cellulose ether polymer and a cellulose esterether polymer. These cellulosic polymers have a degree of substitution. D.S., on the anhydroglucose unit, from greater than 0 up to 3 inclusive. By degree of substitution is meant the average number of hydroxyl groups originally present on the anhydroglucose unit comprising the cellulose polymer that are replaced by a

substituting group. Representative materials include a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkanylates, mono-, di-, and tricellulose aroylates, and the like. Exemplary polymers include cellulose acetate having a D.S. up to 1 and an acetyl content up to 21%; cellulose acetate having a D.S. of 1 to 2 and an acetyl content of 21 to 35 %; cellulose acetate having a D.S. of 2 to 3 and an acetyl content of 35 to 44.8%, and the like. More specific cellulosic polymers include cellulose propionate having a D.S. of 1.8 and a propyl content of 39.2 to 45% and a hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate having a D.S. of 1.8, an acetyl content of 13 to 15% and a butyryl content of 34 to 39%; cellulose acetate butyrate having an acetyl content of 2 to 29%, a butyryl content of 17 to 53% and a hydroxyl content of 0.5 to 4.7; cellulose triacylates having a D.S. of 2.9 to 3 such as cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trisuccinate, and cellulose trioctanoate; cellulose diacylates having a D.S. of 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose dioctanoate, cellulose dipentanoate, co-esters of cellulose such as cellulose acetate butyrate and cellulose acetate propionate, and the like.

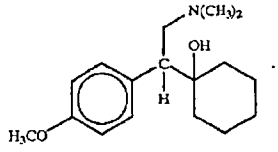
Additional polymers include ethyl cellulose of various degree of etherification with ethoxy content of from 40% to 55%, acetaldehyde dimethyl cellulose acetate, cellulose acetate ethyl carbamate, cellulose acetate methyl carbamate, cellulose acetate diethyl aminoacetate, semipermeable polyamides; semipermeable polyurethanes; semipermeable sulfonated polystyrenes; semipermeable cross-linked selective polymers formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Pat Nos. 3,173,876, 3,276,586, 3,541,005; 3,541,006, and 3,546,142; semipermeable polymers as disclosed by Loeb and Sourirajan in U.S. Pat. No. 3,133,132; semipermeable lightly cross-linked polystyrene derivatives, semipermeable cross-linked poly (sodium styrene sulfonate); semipermeable cross-linked poly(vinylbenzyltrimethyl ammonium chloride); semipermeable polymers exhibiting a fluid permeability of 2.5×10^{-8} to 2.5×10^{-4} (cm^2/hr.atm) expressed per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable wall. The polymers are known to the art in U.S. Pat. Nos. 3,845,770; 3,916,899; and 4,160,020; and in *Handbook of Common Polymers* by Scott, J. R. and Roff, W. J., 1971 published by CRC Press, Cleveland, Ohio.

Compartment **14** comprises a drug composition, identified as drug layer **15** which contains drug **16**, identified by dots. Drug **16** comprises a drug of the following structural formula:



wherein the dotted line represents optional unsaturation or a cycloalkenyl moiety; R_1 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_2 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_4 is a member selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms, formyl, and alkanoyl of 2 to 7 carbon atoms; R_5 and R_6 are independently a member selected from the group consisting of hydrogen, hydroxyl, an alkyd of 1 to 6 carbon atoms, an alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms in which each alkyl group comprises 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, and trifluoroethyl, R_7 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbons, and n is one of the integers 0, 1, 2, 3, and 4. The formula embraces also the pharmaceutically acceptable addition salts including a member selected from the group consisting of inorganic, organic, hydrochloric, hydrobromic, gluconic, fumaric, maleric, sulfonic, succinic, sulfuric, phosphoric, tartaric, acetic, proponic, citric, oxalic and similar pharmaceutically acceptable addition salts. The compounds are known in U.S. Pat. Nos. 4,535,186; 4,611,078; 4,761,501; and 5,190,765.

The drugs of the structural formula are represented by the drug 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol of the structural formula:



The drug embraced by the formula possesses antidepressant properties. The drug in vitro prevents the neuronal uptake of serotonin, morepinephrine, and dopamine and it does not inhibit monoamine oxidase. The drug antagonizes reserpine-induced hypothermia and potentiates the effects of levodopa, and reduces histamine-induced corticotropin release and induces cyclicadenosine monophosphate subsensitivity after both acute and chronic administration. The drug possesses excellent antidepressant activity in humans. The therapeutic amount of drug **16** in dosage form **10** is 0.5 mg to 750 mg, with individual dosage forms comprising 2, 5, 10, 25, 40, 50, 75, 100, 150, 250, 300, 500, and 600 mg of drug **16** for administering in a single dose or in more then one dose over an extended period of 24 hours. The therapeutic properties of the drug embraced by the structural formula are reported in *Current Therapeutic Research*, Vol. 42, No. 5, pages 901 to 909 (1987).

Composition **15** comprising drug **16** may comprise a drug dispensing carrier and composition formulating member consisting of a member selected from the group consisting of 0 wt % to 25 wt % of a hydroxypropylalkylcellulose where alkyl consists of 1 to 7 carbons selected from the group consisting of methyl, ethyl, isopropyl, butyl, pentyl, and hexyl which cellulose member comprises a 9,000 to 1,250,000 molecular weight and is exemplified by hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropylisopropylcellulose, hydroxypropylbutylcellulose and hydroxypropylhexylcellulose represented by dashes **17**; a member selected from the group consisting of 0 wt % to 20 wt % hydroxylalkylcellulose where alkyl is 1 to 6 carbons including methyl, ethyl, propyl, butyl, pentyl, and hexyl which cellulose member comprises a 7,500 to 750,000 molecular weight and is exemplified by hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyisopropylcellulose and

hydroxybutylcellulose as represented by slanted line 18; a member selected from the group consisting of 0 wt % to 35 wt % of a vinyl-polymer having a 3,500 to 750,000 molecular weight represented by poly-n-vinylamide, poly-n-vinlycetamide, poly-n-vinylethylacetamide, poly-n-vinylmethylpropionamide, poly-n-vinyl ethylpropionamide, poly-n-vinylmethylisobutyramide, poly-n-vinyl-2-pyrrolidone, poly-n-vinypiperidone also known as polyvinylpyrrolidone and as poly-n-vinylpyrroledone, poly-n-vinylcaprolactam, poly-n-vinyl-5-methyl-2-pyrrolidone and poly-n-vinyl-3-methyl-2-pyrrolidone, and poly-n-vinylpyrrolidone copolymer with a member selected from the group consisting of vinyl acetate, vinyl alcohol, vinyl chloride, vinyl fluoride, vinyl butyrate, vinyl laurate and vinyl stearate represented by small circles **19**; and 0 wt %, where wt % is weight percent, 35 wt % of a maltodextrin polymer composition comprising the formula $(C_6H_{12}O_5)_n H_2O$ wherein n is 3 to 7,500 and the maltodextrin polymer comprises a 500 to 1,250,000 number average molecular weight represented by a small square **20**; as member selected from the group consisting of 0 wt % to 40 wt % of poly(etheylen oxide) having a molecular weight of 100,000 to 600,000 grams per mole, represented by half-circles **20***a*. Composition **15** optionally comprises from 0 to 4.5 wt % of a lubricant represented by magnesium stearate, calcium stearate or stearic acid. The total weight of all ingredients in composition **15** is equal to 100 wt %, weight percent.

Compartment **14** comprises a displacement composition or push layer **21**. Displacement composition **21** comprises a polymer member selected from the group consisting of a polymer possessing a repeating molecular unit $-(O-CH_2CH_2)_n-$ wherein n is a positive whole number of 50,000 to 300,000 as represented by a poly(alkylene oxide) comprising poly(ethylene oxide) seen as wavy line **22**; a maltodextrin polymer of the formula $(C_6H_{12}O_5)_n H_2O$ wherein n is 50 to 62,000 and comprises a 9,000 to 10,000,000 molecular weight and represented by triangle **23**; a carboxymethylcellulose polymer comprising a 10,000 to 5,000,000 molecular weight represented by alkali carboxymethylcellulose, sodium carboxymethylcellulose and potassium carboxymethylcellulose, ammonium carboxymethylcellulose, sodium carboxymethyl-2-hydroxyethylcellulose, sodium carboxymethylmethylcellulose, alkali carboxymethyl-hydroxypropylmethylcellulose, alkali carboxymethyl-2-hydroxyethylmethylcellulose, alkali carboxymethyl-2-hydroxybutylmethylcellulose, alkali carboxymethyl-2-hydroxyethyl-ethylcellulose and alkali carboxymethyl-2-hydroxypropylcellulose, where alkali is sodium and potassium and seen in drawing FIG. 2 as hexagonal **23***a*. The polymers in push layer **21** provide unforeseen operating advantages as the polymer maintains its chemical composition during operation as it imbibes an external aqueous fluid including biological fluid while simultaneously pushing the drug from the dosage form essentially-free of substantially mixing the drug composition with the push composition. The displacement composition **21** comprises optionally from 4 to 35 wt % of an osmotically active compound, also known as osmagent and represented by vertical line **24**. Representative of osmotically effective compounds comprises salts, oxides, esters that exhibit imbibition properties, carbohydrates and acids including a member selected from the group consisting of magnesium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium chloride, potassium sulfate, sodium sulfate, sodium sulfite, lithium sulfate, ammonium chloride, potassium lactate, mannitol, urea,: magnesium succinate, tartaric acid, raffinose, sorbitol, sucrose, fructose, and glucose. Displacement layer **21** optionally comprises 0.5 wt % to 30 wt % of a cellulose polymer **25** represented by the letter v. Representative of cellulose polymer **25** comprise a member selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropylisopropylcellulose, hydroxypropylbutylcellulose, hydroxypropylpentylcellulose, and hydroxypropylhexylcellulose comprising a 9,000 to 225,000 molecular weight. The displacement composition optionally comprises 0 wt % to 5 wt % of lubricant stearic acid and, magnesium stearate, calcium oleate, oleic acid, and caprylic acid. The polymers are known in U.S. Pat Nos. 3,845,770; and 4,160,020; in *Handbook of Common Polymers* by Scott, J. R., and Roff, W. J., published by CRC Press, Cleveland, Ohio.

Dosage form **10**, a seen in drawing FIG. 3 depicts another preferred manufacture provided by the invention. Dosage form **10**, in drawing FIG. **3**, comprises an external coat on a the exterior surface of dosage form **10**. Coat **26** is a therapeutic composition comprising 10 mg to 150 mg of drug **16**, represented by dots **16**. Exterior coat **26** provides instant drug **16** for instant therapy. Drug **16** is blended with an aqueous-soluble composition comprising a carrier methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and blends of hydroxypropylcellulose and hydroxypropylmethylcellulose. Coat **26** optionally comprises polyethylene glycol or acetylated triglycerides. Coat **26** provides instant therapy as coat **26** dissolves or undergoes dissolution in the presence of a biological fluid and concurrently therewith delivers drug **16** to a drug receiving patient. Coat **26** provides instant therapy and it essentially overcomes the time required for the drug to be delivered from the dosage form.

Dosage form **10**, as provided by this invention, and as seen in the above drawing figures can be manufactured for administering drug **16** by the oral route, and in another embodiment, dosage form **10** comprising exterior and interior drug **16** can be sized and shaped for administering drug **16** by the sublingual and buccal routes. The sublingual and buccal routes can be used for quicker therapy and they can be used when a smaller dose of drug **16** is needed for therapy. The buccal and sublingual routes can be used as a by-pass of the first pass of hepatic metabolism of drug **16**. The sublingual or buccal routes can be used for administering the first dose of drug, followed by permitting dosage form **10** to enter the gastrointestinal tract for subsequent drug delivery.

Dosage form **10**, when manufactured as an osmotic, controlled-release dosage form, comprises at least one passageway **13**, or more than one passageway **13**. The expression "at least one passageway" includes aperture, orifice, bore, pore, porous element through which the drug can be pumped, diffuse, travel or migrate, hollow fiber, capillary tube, porous overlay, porous insert, microporous member, porous composition, and the like. The expression also includes a material that erodes or is leached from wall **12** in the fluid environment of use to produce at least one passageway in dosage form **10**. Representative material suitable for forming at least one passageway, or a multiplicity of passageways, includes an erodible poly(glycolic) acid or poly(lactic) acid member in the wall; a gelatinous filament; poly(vinyl alcohol); leachable materials such as fluid removable pore forming polysaccharides, salts, or oxides, and the like. A passageway or a plurality of passageways can be formed by leaching a material such as sorbitol, sucrose,

lactose, fructose, or the like, from the wall to provide an osmotic dimensioned pore-passageway. The passageway can have any shape such as round, triangular, square, elliptical, and the like, for assisting in the metered release of drug from dosage form **10**. Dosage form **10** can be constructed with one or passageways in spaced apart relation on one or more than a single surface of a dosage form. Passageways and equipment for forming passages are disclosed in U.S. Pat. Nos. 3,845,770 and 3,916,899 by Theeuwes and Higuchi; in U.S. Pat No. 4,063,064 by Saunders et al; and in U.S. Pat. No. 4,088,864 by Theeuwes et al. Osmotic passageways comprising controlled-drug releasing dimension, sized, shaped and adapted as a drug releasing pore formed by aqueous leaching to provide a drug-releasing pore of controlled osmotic release rate are disclosed in U.S. Pat. No. 4,200,098 by Ayer and Theeuwes; and in U.S. Pat. No. 4,285,987 by Ayer and Theeuwes.

Wall **12** of osmotic dosage form **10** can be formed in one technique using the air suspension procedure. This procedure consists in suspending and tumbling the compressed drug-push core laminate in a current of air and wall forming composition until a wall is applied to the drug-push compartment. The air suspension procedure is well-suited for independently forming the wall. The air suspension procedure is described in U.S. Pat. No. 2,799,241; *J. Am. Pharm. Assoc.*, Volume 48, pages 451 to 454, (1959); and ibid, Volume 49, pages 82 to 84, (196). Osmotic dosage forms can also be coated with a wall forming composition in a Wurster® air suspension coater, using methylene dichloride-methanol cosolvent, 80:20, wt:wt, an ethanol-water, or acetone-water cosolvent, 95:5 wt:wt using 2.5 to 4% solids. The Aeromatic® air suspension coater using a methylene dichloride-methanol cosolvent, 80:20 wt:wt, also can be used for applying the wall. Other wall forming techniques such as pan coating system, where wall forming compositions are deposited by successive spraying of the composition on the drug-push compartment, accompanied by tumbling in a rotating pan. Finally, the wall coated compartments are dried in a forced air over at 30° C. to 50° C. for up to a week to free dosage form **10** of solvent. Generally, the walls formed by these techniques have a thickness of 2 to 30 mils with a presently preferred thickness of 4 to 10 mils.

Dosage form **10** of the invention is manufactured by standard manufacturing techniques. For example, in one manufacture the beneficial drug and other ingredients comprising the drug layer facing the exit means are blended and pressed into a solid layer. The drug and other ingredients can be blended with a solvent and mixed into a solid or semisolid formed by conventional methods such a ball-milling, calendering, stirring or rollmilling and then pressed into a preselected shape. The layer possesses dimensions that correspond to the internal dimensions of the area the layer is to occupy in the dosage form and it also possesses dimensions corresponding to the second layer for forming a contacting arrangement therewith. Next, the push layer, is placed in contact with the drug layer. The push layer is manufactured using techniques for providing the drug layer. The layering of the drug layer and the push layer can be fabricated by conventional press-layering techniques. Finally, the two layer compartment forming members are surrounded and coated with an outer wall. A passageway is laser, leached, or mechanically drilled through the wall to contact the drug layer, with the dosage form optically oriented automatically by the laser equipment for forming the passageway on the preselected surface when a laser is used for forming the passageway.

In another manufacture, the dosage form is manufactured by the wet granulation technique. In the wet granulation technique, for example, the drug and the ingredients comprising the drug layer are blended using an organic solvent, such as isopropyl alcohol-ethylene dichloride 80:20 v:v (volume:volume) as the granulation fluid. Other granulating fluid such as denatured alcohol 100% can be used for this purpose. The ingredients forming the drug layer are individually passed through a 40 mesh screen and then thoroughly blended in a mixer. Next, other ingredients comprising the drug layer are dissolved in a portion of the granulation fluid, such as the cosolvent described above. Then the latter prepared wet blend is slowly added to the drug blend with continual mixing in the blender. The granulating fluid is added until a wet blend is produced, which wet mass then is forced through a 20 mesh screen onto oven trays. The blend is dried for 18 to 24 hours at 30° C. to 50° C. The dry granules are sized then with a 20 mesh screen. Next, a lubricant is passed through an 80 mesh screen and added to the dry screen granule blend. The granulation is put into milling jars and mixed on a jar mill for 1 to 15 minutes. The push layer is made by the same wet granulation techniques. The compositions are pressed into their individual layers in a Manesty® press-layer press.

Another manufacturing process that can be used for providing the compartment-forming composition layers comprises blending the powered ingredients for each layer independently in a fluid bed granulator. After the powered ingredients are dry blended in the granulator, a granulating fluid, for example, poly(vinyl-pyrrolidone) in water, or in denatured alcohol, or in 95:5 ethyl alcohol/water, or in blends of ethanol and water is sprayed onto the powders. Optionally, the ingredients can be dissolved or suspended in the granulating fluid. The coated powders are then dried in a granulator. This process granulates all the ingredients present therein while adding the granulating fluid. After the granules are dried, a lubricant such as stearic acid or magnesium stearate is added to the granulator. The granules for each separate layer are pressed then in the manner described above.

The dosage form of the invention is manufactured in another manufacture by mixing a drug with composition forming ingredients and pressing the composition into a solid lamina possessing dimensions that correspond to the internal dimensions of the compartment. In another manufacture the drug and other drug composition-forming ingredients and a solvent are mixed into a solid, or a semisolid, by conventional methods such as ballmilling, calendering, stirring or rollmilling, and then pressed into a preselected layer forming shape. Next, a layer of a composition comprising an osmopolymer and an optional osmagent are placed in contact with the layer comprising the drug. The layering of the first layer comprising the drug and the second layer comprising the osmopolymer and optional osmagent composition can be accomplished by using a conventional layer press technique. The wall can be applied by molding, spraying or dipping the pressed bilayer's shapes into wall forming materials. Another and presently preferred technique that can be used for applying the wall is the air suspension coating procedure. The procedure consists in suspending and tumbling the two layers in current of air until the wall forming composition surrounds the layers. The air suspension procedure is described in U.S. Pat. No. 2,799,241; *J. Am. Pharm. Assoc.*, Vol. 48 pp 451–454 (1979); and, ibid, Vol. 49, pp 82–84 (1960). Other standard manufacturing procedures are described in *Modern Plastics Encyclopedia*, Vol 46, pp 62–70 (1969); and in *Pharmaceu-*

tical Science, by Remington, 14th Ed., pp 1626–1678 (1970), published by Mack Publishing Co., Easton, Pa.

Exemplary solvents suitable for manufacturing the wall, the laminates and laminae include inert inorganic and organic solvents final laminated wall. The solvents broadly include members selected for the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cyclaliphatics, aromatics, heterocyclic solvents and mixtures thereof. Typical solvents include acetone, diacetone, alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptaene ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, carbon tetrachloride, chloroform, nitroethane, nitropropane, tetrachoroethan, ethyl ether, isopropyl ether, cyclohexane, cyclooctane, benzene, toluene, naphtha, tetrahydrofuran, diglyme, aqueous and nonaqueous mixtures thereof, such as acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, and ethylene dichloride and methanol.

DETAILED DISCLOSURE OF EXAMPLES OF THE INVENTION

The following examples are merely illustrative of the present invention and they should not be considered as limiting the scope of the invention in any way as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, the drawings and accompanying claims.

Example 1

A dosage form adapted for delivering a drug in a therapeutic range is manufactured as follows: first a displacement or push layer is prepared by blending and passing through a stainless steel sizing screen having a mesh opening of 420 microns 587.5 grams of sodium carboxymethylcellulose having a degree of polymerization of approximately 3,200 and a degree of substitution of 0.7 carboxymethyl groups per anhydroglucose unit, 300 grams of powdered sodium chloride, 50 grams of hydroxypropylcellulose having a molecular weight of approximately 60,000 grams per mole, and 50 grams of hydroxypropylmethylcellulose having an average methoxyl content of 29 weight percent and an average hydroxypropyl content of 10 weight percent and an average molecular weight of approximately 11,300 grams per mole. Next 10 grams of red ferric oxide were passed through a sizing screen having openings of approximately 250 microns. The resulting powders were mixed in a planetary mixer to a uniform blend. The resulting blend was wet granulated by adding with stirring anhydrous ethyl alcohol until, a cohesive mass was formed. This mass was passed through a sizing screen having openings of approximately 840 microns, forming coated displacement particles, which were an dried overnight at ambient temperature and humidity. The dried particles were then passed again through the 840 micron sizing screen. Next 2.5 grams of magnesium stearate, which had been previously sized through a mesh having 180 micron openings, were tumble mixed into the coated particles.

A composition comprising a drug of the structural formula was prepared as follows: first, a drug composition was prepared by passing 840 grams of venlafaxine hydrochloride, 100 grams of hydroxypropylcellulose having a molecular weight of approximately 60,000 grams per mole, and 50 grams of polyvinylpyrrolidone having a molecular weight of approximately 40,000 grams per mole, were passed through a sizing having openings of approximately 420 microns, and mixed in a planetary mixer to yield a uniform blend. Then, anhydrous ethyl alcohol was added to the mixture with stirring to produce a cohesive damp mass. The resulting damp mass was sized through a sieve having an opening of 840 microns, producing coated venlafaxine drug, which was air dried overnight. The resulting dried coated venlafaxine drug was passed again through the sizing screen having an 840 micron opening. Next, 10 grams of magnesium stearate, sized to 180 microns, was tumble mixed into the blend.

Next, the displacement-push composition and the drug composition were formed into a bilayer core as follows: first, 87 mg of the drug composition was placed in a 9/32 inch round die cavity and lightly tamped with a standard concave round tooling to form a slightly cohesive layer. Then, 70 mg of push composition was added to die and the and the resulting fill was compressed with a final force of 2 tons, thereby forming a two layer cores.

The bilayer cores were placed next in a coating pan having a 12 inch diameter and they were coated with a wall-forming solution. The wall-forming solution was prepared by dissolving 380 grams of cellulose acetate having an acetyl content of 39.8 weight percent in 7,220 grams of acetone. In a separate mixing vessel, 20 grams of polyethylene glycol having a molecular weight of approximately 3,350 grams per mole were dissolved in approximately 380 grams of purified water. The two solutions were mixed to form the wall-coating solution which was spray coated onto the cores until about 20 mg of wall composition was deposited on the surfaces of the bilayer core.

A delivery exit port was formed across the wall by drilling an exit port, centered on the face of the dosage form on the drug composition side of the dosage form. The resulting dosage form was placed in simulated physiological fluid at 37° C., and the dosage form delivered a dose of 73 mg of venlafaxine hydrochloride at a controlled, zero rate over an extended duration of 15 hours.

Example 2

The procedure of Example 1 was followed with the manufacturing procedures as set forth, except that the drug composition comprises 890 grams of venlafaxine hydrochloride, 100 grams of hydroxypropylcellulose, and 10 grams of magnesium stearate. The resulting dosage form released in simulated intestinal fluid 77 mg of venlafaxine hydrochloride at a zero-order rate over an extended duration of 16 hours.

Example 3

The procedure of Example 1 was followed with all manufacturing steps as described, except that the drug composition consists of 650.0 grams of venlafaxine hydrochloride, 240.0 grams of maltodextrin having an average molecular weight of approximately 1800 grams per mole and an average degree of polymerization of 11.1, 80.0 grams of hydroxypropyl cellulose, 20.0 grams of polyvinyl pyrrolidone, and 10.0 grams of magnesium stearate. The resulting dosage form was tested in artificial intestinal fluid, the dosage form delivered a dose of 57 mg of venlafaxine hydrochloride at zero order rate over a period of 15 hours.

Example 4

The procedure of Example 1 was repeated with the manufacture as previously set-forth, except that the drug

composition consists of 840.0 grams of venlafaxine hydrochloride, 150.0 grams of polyethylene oxide having an average molecular weight of approximately 100,000 grams per mole, and 10.0 grams of magnesium stearate. The wall weight weighed approximately 25 mg. The resulting dosage forms were tested in simulated intestinal fluid, and they released a dose of 73 mg of venlafaxine hydrochloride at controlled rate over an extended period of 20 hours.

Example 5

The compositions were manufactured as in Example 1. The process of manufacture was the same except that the push layer manufactured was prepared in a fluid bed aqueous-based granulation process. This was accomplished by sizing the sodium carboxymethyl cellulose, the sodium chloride, the hydroxypropyl cellulose, and red ferric oxide through a screen having openings of 420 microns. The resulting powders were charged into a fluid bed granulation column and binder solution consisting of the hydroxypropyl methylcellulose at a 5 percent solids concentration in water was sprayed on, thereby forming the granules for the push layer.

Example 6

The compositions and processes followed in this example were the same as in Example 1 except the push consisted of 740.0 grams polyethylene oxide with an average molecular weight of approximately 5 million grams per mole, 200.0 grams of sodium chloride, 50.0 grams of hydroxypropyl methyl cellulose having average molecular weight of approximately 11,300 per mole, 5.0 grams of red ferric oxide, and 5.0 grams of magnesium stearate.

DESCRIPTION OF METHOD OF PERFORMING THE INVENTION

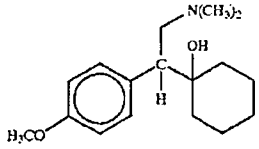
Additional embodiments of the invention pertains to a method for delivering a drug embraced by the structural formula of this invention for its intended therapy. One embodiment pertains to a method for delivering a drug of the formula by administering a dosage form comprising 0.5 mg to 750 mg of the drug from a dosage form selected from sustained-release and controlled-release dosage forms in a therapeutically responsive dose over an extended period of time. Another embodiment of the invention pertains to a method for delivering a drug of the formula disclosed in this invention, to the gastrointestinal tract of a human in need of this therapy, wherein the method comprises the steps of: (A) admitting orally into the gastrointestinal tract of the human a dosage form comprising: (1) a non-toxic wall composition comprising means for imbibing an external aqueous fluid through the wall into the dosage form, which wall surrounds and defines; (2) an internal compartment; (3) a drug composition comprising a drug of the formula in the compartment comprising a dosage unit amount of said drug; (4) a push composition in the compartment for pushing the drug composition from the compartment; (5) at least one exit means in the wall for delivering the drug from the dosage form; (B) imbibing fluid through the wall into the compartment thereby causing the composition to form a deliverable dosage form and concomitantly causing the push composition to expand and push the drug composition through the exit means from the dosage form; and (C) deliver the therapeutic drug in a therapeutically effective amount at a controlled rate over an extended period of time to the patient in need of said therapy. The method also comprising dispensing a dose amount of said drug from an instant release exterior dosage amount of drug to the patient for providing instant anti-depressant therapy.

Inasmuch as the foregoing specification comprises preferred embodiments of the invention, it is understood that variations and modifications may be made herein, in accordance with the inventive principles disclosed, without departing from the scope of the invention.

We claim:

1. A method for administering a drug to the gastrointestinal tract of a human, wherein the method comprises:

(a) admitting orally into the human a dosage form comprising a drug of the formula:



which drug possess antidepressant therapy and the dosage form comprises a member selected from the group consisting of a sustained-release dosage form and a controlled-release dosage form; and,

(b) administering the drug from the dosage form over an extended period of time in a therapeutically responsive dose to produce the antidepressant therapy.

* * * * *

EXHIBIT 2

ENTIRE EXHIBIT UNDER SEAL

EXHIBIT 3

ENTIRE EXHIBIT UNDER SEAL

EXHIBIT 4

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff,	)	Civil Action No.: 06-222 JJF
v.	)	
IMPAX LABORATORIES, INC., Defendant.	)	

DEFENDANT IMPAX LABORATORIES, INC.'S SECOND SET OF INTERROGATORIES (NOS. 20-40)

Pursuant to Federal Rule of Civil Procedure 33, Defendant Impax Laboratories, Inc. ("Impax") requests that Plaintiff Wyeth answer the following interrogatories within 30 days of the date of service hereof. Impax reserves the right to serve additional discovery.

DEFINITIONS

When used in the following interrogatories, the following definitions apply:

1. "WYETH" or "PLAINTIFF" means Plaintiff Wyeth and that company as it was previously named and any related companies, parents, divisions, or subsidiaries, past or present, located in the U.S. or abroad, and the past or present directors, officers, employees, agents, representatives or attorneys thereof.

2. "IMPAX" or "DEFENDANT" means Defendant Impax Laboratories, Inc. and its past or present directors, officers, employees, agents, representatives or attorneys known to WYETH.

3. "CONCERNING" means referring to, relating to, regarding, reflecting, associated with, comprising, constituting, containing, demonstrating, describing,

discussing, evidencing, evincing, indicating, on the subject of, on the topic of, showing, or prepared in connection with the stated matter.

4. "DOCUMENT" or "DOCUMENTS" means all written, printed, typed, electronically produced, electronically stored, photostatic, photographed, recorded, or otherwise reproduced communications or records of every kind and description, whether comprised of letters, words, pictures, sounds, symbols, or combinations thereof. DOCUMENTS include originals as well as drafts, copies, marked-up copies, non-identical duplicates, and computer files, including backup or archival copies. DOCUMENTS include DOCUMENTS created and/or received by WYETH and/or by any of WYETH'S consultants, agents, and/or any other PERSON or PERSONS.

5. "THING" or "THINGS" means any tangible item, including without limitation models, prototypes, research model or sample, and samples of any device or apparatus or product.

6. "DATE" means the exact day, month, and year, if so ascertainable, or if not, the best approximation (including relationship to other events).

7. "PERSON" means any natural person, firm, association, organization, partnership, business, trust, corporation, or public entity.

8. "IDENTIFY" used with respect to a DOCUMENT means to provide: the kind of DOCUMENT (e.g., letter, memo, etc.); the title or name by which the DOCUMENT is referred to; the DATE of the DOCUMENT; the identity of its author or the PERSON creating the DOCUMENT; the identity of each PERSON to whom the DOCUMENT was addressed, sent, or copied; the present location of the original and all copies thereof; the name of the custodian of the DOCUMENT; and a general description of the subject matter.

9. "IDENTIFY" used with respect to a PERSON, means to state:

(a) His, her, or its full name and all known business or other addresses and telephone numbers;

(b) If a natural PERSON, his or her last known residence address and telephone number; and

(c) Such PERSON's relationship to WYETH.

10. "IDENTIFY" used in reference to an act, instance, transaction, occasion, oral discussion, conversation, communication, or event, means to state the DATE upon which and the location at which it occurred, the identity of each PERSON who participated therein or who was present when it occurred, its substance (i.e. what was said and by whom and/or what transpired) and the identity of each DOCUMENT, which, in whole or in part, was the subject of the act or in which it is manifested, referred to or expressed.

11. "PTO" means the United States Patent and Trademark Office.

12. "FDA" means the United States Food and Drug Administration.

13. "NDA" means New Drug Application.

14. "ANDA" means Abbreviated New Drug Application.

15. "INDA" means Investigational New Drug Application.

16. "ORANGE BOOK" means the FDA publication entitled, *Approved Drug Products with Therapeutic Equivalence Evaluations*.

17. "IMPAX'S VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULE" means those pharmaceutical products that are the subject of ANDA No. 78-057.

18. "VENLAFAXINE" means the compound 1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol commonly known as venlafaxine, as well as all compositions, formulations, and preparations containing venlafaxine, including without limitation venlafaxine hydrochloride and other pharmaceutically acceptable salts of venlafaxine.

19. "EFFEXOR" means the VENLAFAXINE product sold by WYETH as Effexor®.

20. "EFFEXOR XR" means the VENLAFAXINE product sold by WYETH as Effexor® XR.

21. "PATENTS IN SUIT" means U.S. Patent No. 6,274,171 B1, U.S. Patent No. 6,403,120 B1, U.S. Patent No. 6,419,958 B2, and any other patent asserted by WYETH as infringed by IMPAX in the above-captioned action, individually or collectively.

22. "NAMED INVENTORS" means Deborah M. Sherman, John C. Clark, John U. Lamer, Steven A. White, and any other person listed as an inventor for the PATENTS IN SUIT, individually or collectively.

23. For the purposes of these interrogatories only, "EXTENDED RELEASE FORMULATION" means a formulation which releases the active ingredient at a slower rate than the immediate release formulation of the active ingredient such that the desired dosing frequency is or would be less than that for the immediate release formulation.

24. "WYETH'S REPLY" means the Plaintiff Wyeth's Reply to First Amended Counterclaims of Defendant Impax Laboratories, Inc. filed by WYETH in the above-captioned action on August 30, 2006, and any amendments thereto.

25. "ALZA" means Alza Corporation, and its past or present directors, officers, employees, agents, representatives or attorneys known to WYETH.

INSTRUCTIONS

A. In responding to these interrogatories, you are required to furnish all information that is available to you or subject to your reasonable inquiry, including information in the possession of your attorneys, accountants, advisors, representatives, agents or other persons directly or indirectly employed by or connected with, you or your attorneys, and anyone else otherwise subject to your control. All documents that respond, in whole or in part, to any portion of the interrogatories below shall be produced in their entirety, including all attachments and enclosures, pursuant to Defendant Impax Laboratories, Inc.'s Third Set of Requests for Production served herewith.

B. In construing these interrogatories, the plural shall include the singular and the singular shall include the plural; a masculine, feminine, or neuter term shall include all other genders; the terms "or," "and," "and/or," and "including" shall be construed conjunctively and inclusively rather than exclusively so as to bring within the scope of the request that which otherwise might be construed as being outside the scope of said request; and the terms "all" and "any" shall be interpreted inclusively so as to mean both "all" and "any" whenever either term is used.

C. Unless otherwise stated, the time period covered by this notice is up to and including the DATE on which answers or amended answers to these interrogatories are served.

D. Pursuant to Federal Rule of Civil Procedure 26(e), these interrogatories are deemed continuing to the fullest extent permissible and to apply to all subsequent actions by you.

E. If you cannot respond to any request in full, you should respond to the fullest extent possible, and explain why you cannot respond to the remainder.

F. Pursuant to Federal Rule of Civil Procedure 26(b)(5), it is not intended that this notice require the disclosure of information that is privileged where such privilege has not been waived. For any information withheld on such grounds, or any other grounds, please provide a written response with the following information:

(i) A description of the information with sufficient particularity to IDENTIFY it for purposes of a court order;

(ii) The DATE stated on which the information first came into existence;

(iii) The nature of the protection claimed;

(iv) A list of all PERSONS with knowledge of the information;

(v) A list of all PERSONS to whom the information was circulated or communicated.

G. In responding to these interrogatories, you must make a diligent search of your records and of other papers or materials in your possession or available to you or your representatives.

H. If any interrogatory is unclear or ambiguous to you, you are requested to contact undersigned counsel as soon as possible so that the interrogatory can be clarified to avoid unnecessary delays in discovery.

INTERROGATORIES

INTERROGATORY NO. 20:

IDENTIFY all electronic systems and databases, including without limitation, their location, the extent to which they are text-searchable, the extent to which they separately have fields and codes for metadata such as date, location, author, recipient, custodian, etc., used or maintained by WYETH or its attorneys that store any electronic media, including without limitation, e-mail, e-mail attachments, word processing files, spreadsheet files, files of scanned DOCUMENTS, PDF files, graphics files, compressed files, CONCERNING the PATENTS IN SUIT, the NAMED INVENTORS, EFFEXOR, EFFEXOR XR, EXTENDED RELEASE FORMULATIONS comprising VENLAFAXINE, NDA 20-699, clinical studies 600B-208-US, 600B-209-US, and 600B-367-EU, or the legal action entitled *Wyeth v. Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd.*, Civil Action No. 03-CV-1293 (WJM) before the United States District Court for the District of New Jersey.

INTERROGATORY NO. 21:

To the extent WYETH contends, or will contend in the event the Court adopts the claim constructions that were found in *Wyeth v. Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd.*, Civil Action No. 03-CV-1293 (WJM), that IMPAX infringes any asserted claim of the PATENTS IN SUIT under the doctrine of equivalents, for each such asserted claim IDENTIFY each claim limitation for which you contend that

IMPAX'S VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULE has an equivalent element, performs an equivalent step, or induces performance of an equivalent step, including factual and legal bases for WYETH's contention, including all PERSONS who have knowledge of such bases, what knowledge each PERSON has, and all DOCUMENTS that evidence such bases.

INTERROGATORY NO. 22:

IDENTIFY the function of the ingredient "microcrystalline cellulose" in any EXTENDED RELEASE FORMULATION comprising VENLAFAXINE claimed in claims 1 through 19 of U.S. Patent No. 6,274,171 and in the methods claimed in claims 3 through 12 of U.S. Patent No. 6,403,120, including all PERSONS who have knowledge of such function, what knowledge each PERSON has, and all DOCUMENTS that evidence such function.

INTERROGATORY NO. 23:

To the extent WYETH contends that IMPAX'S VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULE contains one or more ingredients that are equivalent to microcrystalline cellulose, IDENTIFY the one or more ingredients WYETH contends are equivalent to microcrystalline cellulose, including factual and legal bases for WYETH's contention, including all PERSONS who have knowledge of such bases, what knowledge each PERSON has, and all DOCUMENTS that evidence such bases.

INTERROGATORY NO. 24:

To the extent WYETH contends that IMPAX'S VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULE contains one or more ingredients that are equivalent to microcrystalline cellulose, IDENTIFY the function of

the one or more ingredients WYETH contends are equivalent to microcrystalline cellulose in IMPAX'S VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULE, including factual and legal bases for WYETH's contention, including all PERSONS who have knowledge of such bases, what knowledge each PERSON has, and all DOCUMENTS that evidence such bases.

INTERROGATORY NO. 25:

To the extent WYETH contends that there is a nexus between the commercial success of EFFEXOR XR or other WYETH EXTENDED RELEASE FORMULATIONS comprising VENLAFAXINE and the asserted claims in the PATENTS IN SUIT, such that the commercial success is a secondary consideration of those claims' non-obviousness, IDENTIFY all factual and legal bases for that contention, including all PERSONS who have knowledge of such bases, what knowledge each PERSON has, and all DOCUMENTS that evidence such bases.

INTERROGATORY NO. 26:

To the extent WYETH contends that the following prior art does not anticipate under one or more sections of 35 U.S.C. §102 the asserted claims of the PATENTS IN SUIT, IDENTIFY every limitation of each asserted claim that WYETH contends is not disclosed (expressly or inherently) in each of the following prior art:

(a) EP 0 624 366, published 11/17/1994, "Controlled release formulation containing tramadol"

(b) U.S. Patent No. 6,440,457 B1, "Method of Administering Antidepressant Dosage Form"

(c) WO 94/27589, published 12/8/1994, "Antidepressant dosage form"

(d) AU 47732/90, published 7/12/90, "Sustained release pharmaceutical composition"

(e) WO 95/14460 published 6/1/1995, "Opioid formulations for treating pain"

(f) Troy *et al.*, *J Clin. Pharmacol.* 1995 (April) *35*:404-409, "The pharmacokinetics of venlafaxine when given in a twice-daily regimen"

INTERROGATORY NO. 27:

To the extent WYETH contends that there was no motivation to combine two or more of the following prior art at the time of the asserted claims' date(s) of conception, IDENTIFY all factual and legal bases for such contention, including all PERSONS who have knowledge of such bases, what knowledge each PERSON has, and all DOCUMENTS that evidence such bases:

(a) EP 0 624 366, published 11/17/1994, "Controlled release formulation containing tramadol"

(b) U.S. Patent No. 6,440,457 B1, "Method of Administering Antidepressant Dosage Form"

(c) WO 94/27589, published 12/8/1994, "Antidepressant dosage form"

(d) AU 47732/90, published 7/12/90, "Sustained release pharmaceutical composition"

(e) WO 95/14460 published 6/1/1995, "Opioid formulations for treating pain"

(f) Troy *et al.*, *J Clin. Pharmacol.* 1995 (April) *35*:404-409, "The pharmacokinetics of venlafaxine when given in a twice-daily regimen"

INTERROGATORY NO. 28:

IDENTIFY all factual and legal bases on which WYETH relies in its denials in paragraphs 1, 4-5, 7-36, 38, 40-47, 49-57 of WYETH'S REPLY, including all PERSONS who have knowledge of such bases, what knowledge each PERSON has, and all DOCUMENTS that evidence such bases.

INTERROGATORY NO. 29:

IDENTIFY all studies, tests, trials, research, or experiments conducted prior to July 16, 2002, including all PERSONS who have knowledge of such studies, tests, trials,

research, or experiments, what knowledge each PERSON has, and all DOCUMENTS that evidence such studies, tests, trials, research, or experiments, that compare incidences of nausea and emesis between patients receiving EFFEXOR and patients receiving EFFEXOR XR or any WYETH EXTENDED RELEASE FORMULATION comprising VENLAFAXINE.

INTERROGATORY NO. 30:

To the extent WYETH contends that any part or all of the following passage:

> The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

from the PATENTS IN SUIT was not material to patentability and/or was a representation made to the PTO without the intent to deceive, IDENTIFY all factual and legal bases for such contentions, including all PERSONS who have knowledge of such bases, what knowledge each PERSON has, and all DOCUMENTS that evidence such bases.

INTERROGATORY NO. 31:

IDENTIFY all factual and legal bases, including all PERSONS who have knowledge of such bases, what knowledge each PERSON has, and all DOCUMENTS that evidence such bases, for WYETH's statements in paragraphs 18, 19, and 21 of

WYETH'S REPLY that "during the prosecution of the patents-in-suit, Wyeth never represented to the PTO that each clinical study, standing alone, established a statistically significant improvement of Effexor® XR over immediate release Effexor.®"

INTERROGATORY NO. 32:

IDENTIFY all factual and legal bases, including all PERSONS who have knowledge of such bases, what knowledge each PERSON has, and all DOCUMENTS that evidence such bases, for WYETH's denial of paragraph 68 of IMPAX's Counterclaims, as stated in paragraph 20 of WYETH'S REPLY.

INTERROGATORY NO. 33:

To the extent WYETH contends that WYETH or the NAMED INVENTORS were not aware of an article by Lynn A. Cunningham, M.D., entitled *Once-Daily Venlafaxine Extended Release (XR) and Venlafaxine Immediate Release (IR) in Outpatients with Major Depression*, published in volume 9, no. 3 of the Annals of Clinical Psychiatry in 1997 during the prosecution of the PATENTS IN SUIT, that this article was not material to patentability, and/or that this article was not withheld from the PTO with the intent to deceive, IDENTIFY all factual and legal bases for such contentions, including all PERSONS who have knowledge of such bases, what knowledge each PERSON has, and all DOCUMENTS that evidence such bases.

INTERROGATORY NO. 34:

IDENTIFY all relationships, agreements, pacts, engagements, or understandings prior to July 16, 2002 between WYETH and ALZA CONCERNING ALZA's research and development of an EXTENDED RELEASE FORMULATION comprising VENLAFAXINE, including all PERSONS who have knowledge of these relationships,

agreements, pacts, engagements, or understandings, what knowledge each PERSON has, and all DOCUMENTS that evidence these relationships, agreements, pacts, engagements, or understandings.

INTERROGATORY NO. 35:

To the extent WYETH contends that, during the prosecution of the PATENTS IN SUIT, WYETH or the NAMED INVENTORS were not aware of ALZA's development of an EXTENDED RELEASE FORMULATION comprising VENLAFAXINE beyond the disclosure in publication WO 94/27589, that the information known about ALZA's development was not material to patentability, and/or that information known about ALZA's development was not withheld from the PTO with the intent to deceive, IDENTIFY all factual and legal bases for such contentions, including all PERSONS who have knowledge of such bases, what knowledge each PERSON has, and all DOCUMENTS that evidence such bases, for WYETH's contention.

INTERROGATORY NO. 36:

To the extent WYETH contends that the following passage:

> It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble.

from the PATENTS IN SUIT was not material to patentability and/or was not made to the PTO with the intent to deceive, IDENTIFY all factual and legal bases for such contention, including all PERSONS who have knowledge of such bases, what knowledge each PERSON has, and all DOCUMENTS that evidence such bases.

INTERROGATORY NO. 37:

To the extent WYETH contends that the asserted claims of the PATENTS IN SUIT are not obvious in view of the development of WYETH's Inderal® LA (propranolol HCl) Long-Acting Capsules, IDENTIFY all factual and legal bases for that contention, including all PERSONS who have knowledge of such bases, what knowledge each PERSON has, and all DOCUMENTS that evidence such bases.

INTERROGATORY NO. 38:

IDENTIFY all studies, tests, trials, research, or experiments WYETH conducted prior to July 16, 2002, including all PERSONS who have knowledge of such studies, tests, trials, research, and experiments, what knowledge each PERSON has, and all DOCUMENTS that evidence such studies, tests, trials, research, or experiments, that compare chemical properties, including without limitation solubility, of propranolol and its salts, with that of VENLAFAXINE and its salts.

INTERROGATORY NO. 39:

To the extent WYETH contends that analysis, study, test, trial, research, or experimental results prior to March 25, 1996 demonstrated that the EXTENDED RELEASE FORMULATION comprising VENLAFAXINE claimed in the PATENTS IN SUIT provided a therapeutic blood plasma concentration of VENLAFAXINE over a twenty-four hour period with diminished incidences of nausea and emesis, IDENTIFY such results and all other factual and legal bases for WYETH's contention, including all PERSONS who have knowledge of such bases, what knowledge each PERSON has, and all DOCUMENTS that evidence such bases.

INTERROGATORY NO. 40:

To the extent WYETH contends that analysis, study, test, trial, research, and experimental results prior to March 25, 1996 demonstrated that the EXTENDED RELEASE FORMULATION comprising VENLAFAXINE claimed in the PATENTS IN SUIT eliminated the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of VENLAFAXINE, IDENTIFY those results and all other factual and legal bases, including all DOCUMENTS including all PERSONS who have knowledge of such bases, what knowledge each PERSON has, and all DOCUMENTS that evidence such bases, for WYETH's contention.

Dated: September 8, 2006

MARY B. MATTERER (I.D. No. 2696)
MORRIS JAMES HITCHENS & WILLIAMS LLP
222 Delaware Ave., 10th Floor
Wilmington, DE 19801
Telephone: (302) 888-6800
mmatterer@morrisjames.com

M. PATRICIA THAYER (*pro hac vice*)
JOHN M. BENASSI (*pro hac vice*)
JESSICA R. WOLFF (*pro hac vice*)
SAMUEL F. ERNST (*pro hac vice*)
HELLER EHRMAN LLP
4350 La Jolla Village Drive, 7th Floor
San Diego, CA 92101
Telephone: (858) 450-8400
Facsimile: (858) 450-8499

Attorneys for Defendant
IMPAX LABORATORIES, INC.

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EXHIBIT 5

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 31/135, 9/00, 9/20

A2

(11) International Publication Number: WO 94/27589

(43) International Publication Date: 8 December 1994 (08.12.94)

(21) International Application Number: PCT/US94/06049

(22) International Filing Date: 27 May 1994 (27.05.94)

(30) Priority Data:
068,480 27 May 1993 (27.05.93) US

(71) Applicant: ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).

(72) Inventors: EDGREN, David, E.; 261 Francisco Street, El Granada, CA 94018 (US). BHATTI, Gurdish, Kaur; 46744 Rancho Higuera, Fremont, CA 94539 (US). HATAMKHANI, Zahedeh; 44918 Parkmeadow Drive, Fremont, CA 94539 (US). WONG, Patrick, S.-L.; 2030 Cornell Street, Palo Alto, CA 94303 (US).

(74) Agents: SABATINE, Paul, L. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).

(81) Designated States: AU, CA, FI, JP, KR, NO, NZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, NL, PT, SE).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: ANTIDEPRESSANT DOSAGE FORM

(57) Abstract

The invention pertains to a dosage form (10) and to administering an antidepressant medicament (16) for an extended period of time in a rate-known dose.

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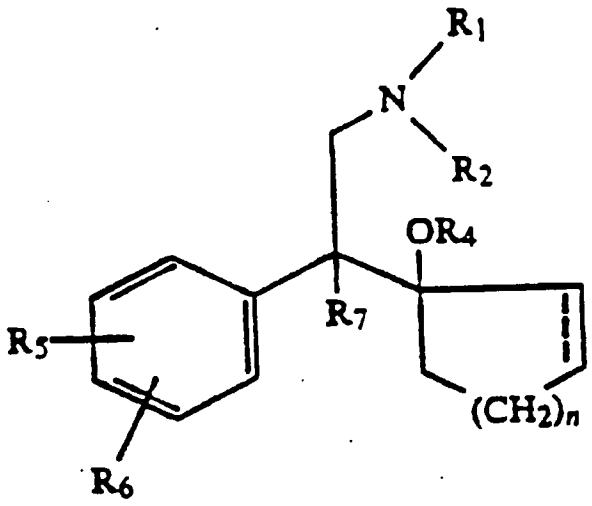
ANTIDEPRESSANT DOSAGE FORM

FIELD OF THE INVENTION

This invention pertains to a controlled-release dosage form comprising a compound of the following structural formula:



useful for antidepressant therapy. The invention concerns also a method useful for antidepressant therapy by administering the controlled-release dosage form comprising the compound of the formula.

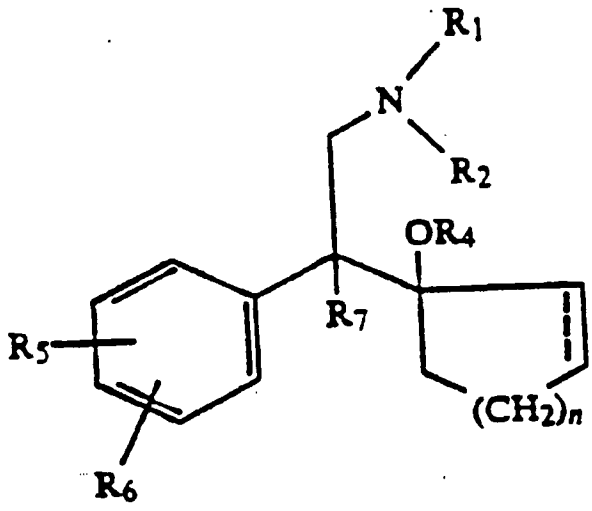
BACKGROUND OF THE INVENTION

The primary goal of drug administration is to provide a therapeutic dose of drug in the body to achieve a desired blood concentration, and then maintain the desired drug blood concentration. The prior art, in attempts to obtain the desired therapeutic effect, often used different dosage forms or programs. One dosage program consists of a single dosing of the drug from a conventional capsule or tablet that produced a

rapid rise followed by an immediate decline of the drug blood level versus time. The single dosing does not maintain the drug within a therapeutic range for an extended period of time, but exhibits of a short duration of action due to the inability of the conventional dosage form to provide drug delivery over time.

Another prior art dosing program used to obtain and to achieve drug blood levels consists in administering the drug repetitively using conventional dosage forms at various dosing intervals, as in multiple-dose therapy. In administering a drug according to the multiple-dose therapy, the drug blood level reached and the time required to reach that level depends on the dose and the dosing interval. There are, however, several potential problems inherent in multiple dose therapy. For example, if the dosing interval is not appropriate for the biological half-life of the drug, large peaks and valleys may result in the drug blood levels. Also, the drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for many disease states. And too, patient noncompliance with the multiple dosing regimen can result in a failure of this approach, especially as a drug in circulation surges to a high each time the drug is administered followed by a decline in drug concentration in the blood and in body compartments. Thus, a graph of drug in circulation following a dosage program of several doses, has an appearance of a series of peaks, which may surpass the toxic threshold. Then, each time the blood levels decreases into valleys, below a critical level needed to achieve a desired therapeutic effect, that effect may not be obtainable in the blood and body. Conventional dosage forms and their mode of operation are discussed in Remington's Pharmaceutical Sciences, 18th Edition, pages 1676 to 1686, (1990), Mack Publishing Co.; The Pharmacological Basis of Therapeutics, 7th Edition, page 7 (1985) published by MacMillian Publishing Co., and in United States Pat. Nos. 3,598,122 and 3,598,123 both issued to Zaffaroni.

A critical need exists for a controlled-rate dosage form for administering the drug of the formula:



which drug is presently administered in conventional dosage forms including tablets, capsules, elixirs and suspensions. These conventional dosage forms produce the peaks and valleys drug pattern presented above and they do not provide for controlled-rate therapy over an extended period of time. The drug of the formula is dosed twice or thrice a day now because of its elimination half-life of three to five hours. This pattern of dosing indicates the need for a controlled-release dosage form that can administer the drug at a controlled rate over an extended time to provide constant therapy and thereby eliminate the need for multiple

dosing. The drugs of the structural formula are known in United States Patent Nos. 4,535,186; 4,611,078; and 4,761,501 all issued to Husbands, Yardley and Muth.

The prior art provided controlled-release dosage forms that can continuously over time administer a drug for controlled-rate therapy. For example, in United States Pat. No. 4,327,725 issued to Cortese and Theeuwes and in United States Pat. Nos. 4,612,008; 4,765,989; and 4,783,337 issued to Wong, Barclay, Deters, and Theeuwes. The dosage forms disclosed in these patents provide a drug at a constant rate for effecting a therapeutic range for preferred therapy. The dosage forms of the patents provide a therapeutic range and avoids delivering the drug in excess in a toxic range with its accompanying side-effects. The dosage forms of the patents in providing a controlled dose in a therapeutic range also avoids delivering the drug in an ineffective dose in an ineffective range.

The dosage forms presented immediately above operate successfully for their intended use and they can deliver many drugs indicated for good therapy. The drugs of the above structural formula, however, possess properties such as a high solubility of 570 mg per ml at a body temperature of 37°C. that can lead to a premature release of the drug from the dosage form. During operation of the dosage forms, the convection motion of the imbibed fluid, and the hydrostatic pressure of the imbibed fluid coupled with the high solubility can result in the premature release of the drugs of the formula.

It is immediately apparent in the light of the above presentation that an urgent need exists for a dosage form endowed with controlled-release delivery for delivering the drugs embraced by the structural formula. The need exists for the dosage form for delivering the drug at a

controlled dose in a therapeutic range while simultaneously providing the intended therapy. It will be appreciated by those versed in the dispensing art, that such a dosage form that can administer the drug in a controlled-rate dose over time, would, represent an advancement and a valuable contribution to the art.

OBJECTS OF THE INVENTION

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide a dosage from that possesses controlled-release delivery for providing a dosage form for administering a drug of the structural formula.

Another object of the present invention is to provide a dosage form for administering the drug of the formula in a controlled-rate dose in a therapeutic range over a prolonged period of time.

Another object of the present invention is to provide a dosage form that can deliver the drug of the formula essentially-free of a premature release from the dosage form.

Another object of the present invention is to provide a drug delivery controlled-release system that can deliver a drug for maintaining constant drug levels in the blood thereby functioning as a prolonged release system.

Another object of the present invention is to provide drug delivery sustained-release system that provides slow release of the drug over an extended period of time optionally in a therapeutic range.

Another object of the present invention is to provide a dosage form that substantially reduces and/or substantially eliminates the unwanted influences of a gastrointestinal environment of use and still provides controlled drug administration.

Another object of the present invention is to provide an improvement in a dosage form for administering a drug embraced by the structural formula and its pharmaceutically acceptable salt, wherein the improvement comprises delivering the drug in a controlled-release rate from the dosage form for improved and known therapy.

Another object of the invention is to provide a once-a-day controlled-release dosage form to deliver the drug of the structural formula orally to a patent in need of therapy.

Another object of the invention is to provide a method for administering a drug of the formula by orally administering the drug in a controlled rate dose per unit dose over an extended time to an animal in need of therapy.

Another object of the present invention is to provide a method for administering a drug of the formula in a therapeutic range while simultaneously substantially-avoiding a toxic range and an infective range.

Another object of the present invention is to provide a therapeutic composition comprising a drug of the structural formula blended with a drug-composition forming polymer.

Another object of the invention is to provide a therapeutic composition comprising a member selected from the group consisting of

venlafaxine and its pharmaceutically acceptable additional salt and a pharmaceutically acceptable polymer carrier for venlafaxine and its acceptable salts.

Other objects, feature, and advantages of the invention will more apparent to those versed in the dispensing arts from the following detailed specification, taken in conjunction with the drawings and the accompanying claims.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawing figures, which are not drawn to scale, but are set forth to illustrate various embodiments of the invention, the drawing figures are as follows:

Drawing Figure 1 is a general view of a dosage form provided by the invention, which dosage form is designed and shaped for oral administration, and for a drug delivery in a controlled-rate dose in the gastrointestinal tract;

Drawing Figure 2 is an opened view of the dosage form of drawing Figure 1 for depicting the structure of the dosage form and the composition member contained inside the dosage form; and

Drawing Figure 3 is a view of a dosage form that depicts an external, instant-release of drug of the structural formula coated on the exterior surface of the dosage form.

In the drawing figures, and in the specification, like parts in related figures are identified by like numbers. The terms appearing earlier in the

specification and in the description of the drawing figures, as well as embodiments thereof, are further described elsewhere in the disclosure.

DETAILED DESCRIPTION OF THE DRAWINGS

Turning now to the drawing figures in detail, which drawing figures are examples of dosage forms provided by this invention, and which examples are not to be construed as limiting, one example of a dosage form is seen in drawing Figure 1. In drawing Figure 1, a dosage form 10 is seen comprising a body member 11, which body 11 comprises wall 12, that surrounds and forms an internal area, not seen in drawing Figure 1. Dosage form 10 comprises at least one exit port 13 for connecting the exterior with the interior of dosage form 10.

The dosage form 10 of drawing Figure 1 illustrates a controlled-release dosage form manufactured as an osmotic dosage form that delivers a drug by osmotic action over an extended period of time. The dosage form comprising controlled-release properties embraced by this invention are successful at maintaining substantially constant drug levels in the blood or in a tissue. The dosage forms within the mode and manner of this invention comprises also sustained-release dosage forms. The sustained-release dosage forms releases the drug and provide drug levels in the blood or target tissue within a therapeutic range over an extended period of time. The invention embraces additionally prolonged release dosage forms. The prolonged release dosage form denotes extended duration of drug delivery action over that achieved by conventional drug delivery.

In drawing Figure 2, dosage form 10 of Figure 1 is seen in opened section. In drawing Figure 2, dosage form 10 comprises a body 11, a wall 12 that surrounds and defines an internal compartment 14. In

drawing Figure 2, internal compartment 14 communicates through an exit passageway 13 with the exterior of dosage form 10.

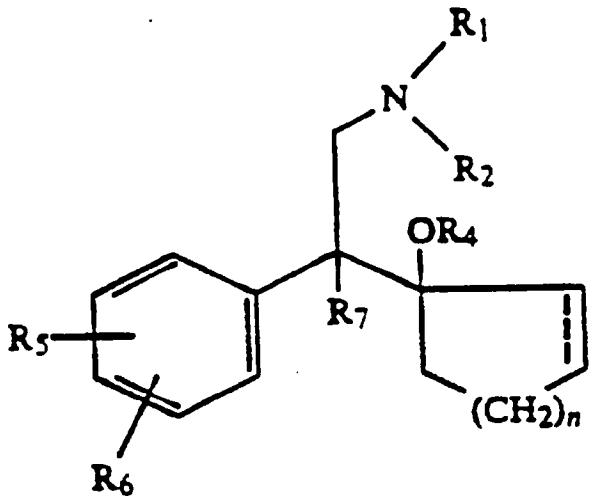
Wall 12 of dosage form 10 comprises totally or in at least a part of a composition that is permeable to the passage of an exterior fluid present in an environment of use, such as aqueous and biological fluids. Wall 12 is formed of nontoxic ingredients, is substantially impermeable to the passage of a drug and other ingredients present in compartment 14. Wall 12 comprises a composition that is substantially inert, that is, wall 12 maintains its physical and chemical integrity during the drug dispensing life of a drug from dosage form 10. The phrase, "maintaining its physical and chemical integrity," means wall 12 does not lose its structure and it does not change during the dispensing life of dosage form 10, except for possible leaching of one or more exit 13 passageway formed during operation of dosage form 10 or for leaching a water-soluble flux enhancers blended into wall 12. Wall 12 comprises a material that does not adversely affect an animal, a human or any other components comprising the dosage form. Representative materials for forming wall 12, are in one embodiment, a cellulose ester polymer, a cellulose ether polymer and a cellulose esterether polymer. These cellulosic polymers have a degree of substitution. D.S., on the anhydroglucose unit, from greater than 0 up to 3 inclusive. By degree of substitution is meant the average number of hydroxyl groups originally present on the anhydroglucose unit comprising the cellulose polymer that are replaced by a substituting group. Representative materials include a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkanylates, mono-,di-, and tricellulose aroylates, and the like. Exemplary polymers include cellulose acetate having a D.S. up to 1 and an acetyl content up to 21%; cellulose acetate having a D.S. of 1 to 2 and an acetyl content of 21 to 35 %;

cellulose acetate having a D.S. of 2 to 3 and an acetyl content of 35 to 44.8%, and the like. More specific cellulosic polymers include cellulose propionate having a D.S. of 1.8 and a propyl content of 39.2 to 45% and a hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate having a D.S. of 1.8, an acetyl content of 13 to 15% and a butyryl content of 34 to 39%; cellulose acetate butyrate having an acetyl content of 2 to 29%, a butyryl content of 17 to 53% and a hydroxyl content of 0.5 to 4.7; cellulose triacylates having a D.S. of 2.9 to 3 such as cellulose trivalerate, cellulose trilaurate, cellulose tripolmitate, cellulose trisuccinate, and cellulose trioctanoate; cellulose diacylates having a D.S. of 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose dioctanoate, cellulose dipentanoate, co-esters of cellulose such as cellulose acetate butyrate and cellulose acetate propionate, and the like.

Additional polymers include ethyl cellulose of various degree of etherification with ethoxy content of from 40% to 55%, acetaldehyde dimethyl cellulose acetate, cellulose acetate ethyl carbamate, cellulose acetate methyl carbamate, cellulose acetate diethyl aminoacetate, semipermeable polyamides; semipermeable polyurethanes; semipermeable sulfonated polystyrenes; semipermeable cross-linked selective polymers formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Pat Nos. 3,173,876, 3,276,586, 3,541,005; 3,541,006, and 3,546,142; semipermeable polymers as disclosed by Loeb and Sourirajan in U.S. Pat. No. 3,133,132; semipermeable lightly cross-linked polystyrene derivatives, semipermeable cross-linked poly(sodium styrene sulfonate); semipermeable cross-linked poly(vinylbenzyltrimethyl ammonium chloride); semipermeable polymers exhibiting a fluid permeability of 2.5×10^{-8} to 2.5×10^{-4} (cm^2/hr.atm) expressed per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable wall. The polymers are known to the art in U.S. Pat. Nos. 3,845,770; 3,916,899; and 4,160,020; and in Handbook

of Common Polymers by Scott, J. R. and Roff, W. J., 1971 published by CRC Press, Cleveland, OH.

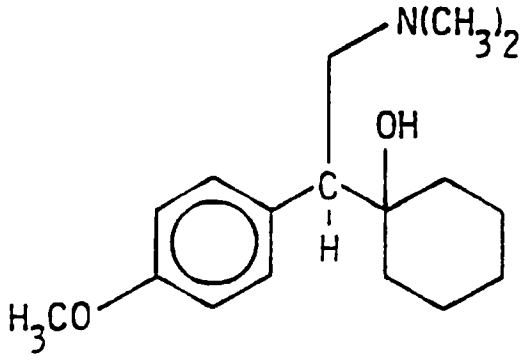
Compartment 14 comprises a drug composition, identified as drug layer 15 which contains drug 16, identified by dots. Drug 16 comprises a drug of the following structural formula:



wherein the dotted line represents optional unsaturation or a cycloalkenyl moiety; R_1 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_2 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_4 is a member selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms, formyl, and alkanoyl of 2 to 7 carbon atoms; R_5 and R_6 are independently a member selected from the group consisting of hydrogen, hydroxyl, an alkyl of 1 to 6 carbon atoms, an alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms in which each alkyl group comprises 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon

atoms, halo, and trifluoroethyl, R_7 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbons, and n is one of the integers 0, 1, 2, 3, and 4. The formula embraces also the pharmaceutically acceptable addition salts including a member selected from the group consisting of inorganic, organic, hydrochloric, hydrobromic, gluconic, fumaric, maleric, sulfonic, succinic, sulfuric, phosphoric, tartaric, acetic, proponic, citric, oxalic and similar pharmaceutically acceptable addition salts. The compounds are known in U.S. Pat. Nos. 4,535,186; 4,611,078; 4,761,501; and 5,190,765.

The drugs of the structural formula are represented by the drug 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol of the structural formula:



The drug embraced by the formula possesses antidepressant properties. The drug in vitro prevents the neuronal uptake of serotonin, morepinephrine, and dopamine and it does not inhibit monoamine oxidase. The drug antagonizes reserpine-induced hypothermia and potentiates the effects of levodopa, and reduces histamine-induced

corticotropin release and induces cyclicadenosine monophosphate subsensitivity after both acute and chronic administration. The drug possesses excellent antidepressant activity in humans. The therapeutic amount of drug 16 in dosage form 10 is 0.5 mg to 750 mg, with individual dosage forms comprising 2, 5, 10, 25, 40, 50, 75, 100, 150, 250, 300, 500, and 600 mg of drug 16 for administering in a single dose or in more then one dose over an extended period of 24 hours. The therapeutic properties of the drug embraced by the structural formula are reported in Current Therapeutic Research, Vol. 42, No. 5, pages 901 to 909 (1987).

Composition 15 comprising drug 16 may comprise a drug dispensing carrier and composition formulating member consisting of a member selected from the group consisting of 0 wt% to 25 wt% of a hydroxypropylalkylcellulose where alkyl consists of 1 to 7 carbons selected from the group consisting of methyl, ethyl, isopropyl, butyl, pentyl, and hexyl which cellulose member comprises a 9,000 to 1,250,000 molecular weight and is exemplified by hydroxypropylmethylcelluose, hydroxypropylethylcellulose, hydroxypropylisopropylcellulose, hydroxypropylbutylcellulose and hydroxypropylhexylcellulose represented by dashes 17; a member selected from the group consisting of 0 wt% to 20 wt% hydroxylalkylcellulose where alkyl is 1 to 6 carbons including methyl, ethyl, propyl, butyl, pentyl, and hexyl which cellulose member comprises a 7,500 to 750,000 molecular weight and is exemplified by hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyisopropylcellulose and hydroxybutylcellulose as represented by slanted line 18; a member selected from the group consisting of 0 wt% to 35 wt% of a vinyl-polymer having a 3,500 to 750,000 molecular weight represented by poly-n-vinylamide, poly-n-vinlycetamide, poly-n-vinylethylacetamide, poly-n-vinylmethylpropionamide, poly-n-vinyl

ethylpropionamide, poly-n-vinylmethylisobutyramide, poly-n-vinyl-2-pyrrolidone, poly-n-vinypiperidone also known as polyvinylpyrrolidone and as poly-n-vinylpyrroledone, poly-n-vinylcaprolactam, poly-n-vinyl-5-methyl-2-pyrrolidone and poly-n-vinyl-3-methyl-2-pyrrolidone, and poly-n-vinylpyrrolidone copolymer with a member selected from the group consisting of vinyl acetate, vinyl alcohol, vinyl chloride, vinyl fluoride, vinyl butyrate, vinyl laurate and vinyl stearate represented by small circles 19; and 0 wt%, where wt% is weight percent, 35 wt% of a maltodextrin polymer composition comprising the formula $(C_6H_{12}O_5)_n H_2O$ wherein n is 3 to 7,500 and the maltodextrin polymer comprises a 500 to 1,250,000 number average molecular weight represented by a small square 20; as member selected from the group consisting of 0 wt% to 40 wt% of poly(etheylen oxide) having a molecular weight of 100,000 to 600,000 grams per mole, represented by half-circles 20a. Composition 15 optionally comprises from 0 to 4.5 wt% of a lubricant represented by magnesium stearate, calcium stearate or stearic acid. The total weight of all ingredients in composition 15 is equal to 100 wt%, weight percent.

Compartment 14 comprises a displacement composition or push layer 21. Displacement composition 21 comprises a polymer member selected from the group consisting of a polymer possessing a repeating molecular unit $-(-O-CH_2CH_2-)_n$ wherein n is a positive whole number of 50,000 to 300,000 as represented by a poly(alkylene oxide) comprising poly(ethylene oxide) seen as wavy line 22; a maltodextrin polymer of the formula $(C_6H_{12}O_5)_n H_2O$ wherein n is 50 to 62,000 and comprises a 9,000 to 10,000,000 molecular weight and represented by triangle 23; a carboxymethylcellulose polymer comprising a 10,000 to 5,000,000 molecular weight represented by alkali carboxymethylcellulose, sodium carboxymethylcellulose and potassium carboxymethylcellulose, ammonium carboxymethylcellulose, sodium carboxymethyl-2-hydroxyethylcellulose, sodium carboxymethyl-methylcellulose, alkali

carboxymethyl-hydroxypropyl-methylcellulose, alkali carboxymethyl-2-hydroxyethylmethylcellulose, alkali carboxymethyl-2-hydroxybutylmethylcellulose, alkali carboxymethyl-2-hydroxyethyl-ethylcellulose and alkali carboxymethyl-2-hydroxypropylcellulose, where alkali is sodium and potassium and seen in drawing Figure 2 as hexagonal 23a. The polymers in push layer 21 provide unforeseen operating advantages as the polymer maintains its chemical composition during operation as it imbibes an external aqueous fluid including biological fluid while simultaneously pushing the drug from the dosage form essentially-free of substantially mixing the drug composition with the push composition. The displacement composition 21 comprises optionally from 4 to 35 wt% of an osmotically active compound, also known as osmagent and represented by vertical line 24. Representative of osmotically effective compounds comprises salts, oxides, esters that exhibit imbibition properties, carbohydrates and acids including a member selected from the group consisting of magnesium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium chloride, potassium sulfate, sodium sulfate, sodium sulfite, lithium sulfate, ammonium chloride, potassium lactate, mannitol, urea, magnesium succinate, tartaric acid, raffinose, sorbitol, sucrose, fructose, and glucose. Displacement layer 21 optionally comprises 0.5 wt % to 30 wt% of a cellulose polymer 25 represented by the letter v. Representative of cellulose polymer 25 comprise a member selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropylisopropylcellulose, hydroxypropylbutylcellulose, hydroxypropylpentylcellulose, and hydroxypropylhexylcellulose comprising a 9,000 to 225,000 molecular weight. The displacement composition optionally comprises 0 wt% to 5 wt% of lubricant stearic acid and, magnesium stearate, calcium oleate, oleic acid, and caprylic acid. The polymers are known in U.S. Pat Nos.

3,845,770; and 4,160,020; in Handbook of Common Polymers by Scott, J. R., and Roff, W. J., published by CRC Press, Cleveland, OH.

Dosage form 10, a seen in drawing Figure 3 depicts another preferred manufacture provided by the invention. Dosage form 10, in drawing Figure 3, comprises an external coat on a the exterior surface of dosage form 10. Coat 26 is a therapeutic composition comprising 10 mg to 150 mg of drug 16, represented by dots 16. Exterior coat 26 provides instant drug 16 for instant therapy. Drug 16 is blended with an aqueous-soluble composition comprising a carrier methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and blends of hydroxypropylcellulose and hydroxypropylmethylcellulose. Coat 26 optionally comprises polyethylene glycol or acetylated triglycerides. Coat 26 provides instant therapy as coat 26 dissolves or undergoes dissolution in the presence of a biological fluid and concurrently therewith delivers drug 16 to a drug receiving patient. Coat 26 provides instant therapy and it essentially overcomes the time required for the drug to be delivered from the dosage form.

Dosage form 10, as provided by this invention, and as seen in the above drawing figures can be manufactured for administering drug 16 by the oral route, and in another embodiment, dosage form 10 comprising exterior and interior drug 16 can be sized and shaped for administering drug 16 by the sublingual and buccal routes. The sublingual and buccal routes can be used for quicker therapy and they can be used when a smaller dose of drug 16 is needed for therapy. The buccal and sublingual routes can be used as a by-pass of the first pass of hepatic metabolism of drug 16. The sublingual or buccal routes can be used for administering the first dose of drug, followed by permitting dosage form 10 to enter the gastrointestinal tract for subsequent drug delivery.

Dosage form 10, when manufactured as an osmotic, controlled-release dosage form, comprises at least one passageway 13, or more than one passageway 13. The expression "at least one passageway" includes aperture, orifice, bore, pore, porous element through which the drug can be pumped, diffuse, travel or migrate, hollow fiber, capillary tube, porous overlay, porous insert, microporous member, porous composition, and the like. The expression also includes a material that erodes or is leached from wall 12 in the fluid environment of use to produce at least one passageway in dosage form 10. Representative material suitable for forming at least one passageway, or a multiplicity of passageways, includes an erodible poly(glycolic) acid or poly(lactic) acid member in the wall; a gelatinous filament; poly(vinyl alcohol); leachable materials such as fluid removable pore forming polysaccharides, salts, or oxides, and the like. A passageway or a plurality of passageways can be formed by leaching a material such as sorbitol, sucrose, lactose, fructose, or the like, from the wall to provide an osmotic dimensioned pore-passageway. The passageway can have any shape such as round, triangular, square, elliptical, and the like, for assisting in the metered release of drug from dosage form 10. Dosage form 10 can be constructed with one or passageways in spaced apart relation on one or more than a single surface of a dosage form. Passageways and equipment for forming passages are disclosed in U.S. Pat. Nos. 3,845,770 and 3,916,899 by Theeuwes and Higuchi; in U.S. Pat No. 4,063,064 by Saunders et al; and in U.S. Pat. No. 4,088,864 by Theeuwes et al. Osmotic passageways comprising controlled-drug releasing dimension, sized, shaped and adapted as a drug releasing pore formed by aqueous leaching to provide a drug-releasing pore of controlled osmotic release rate are disclosed in U.S. Pat. No. 4,200,098 by Ayer and Theeuwes; and in U.S. Pat. No. 4,285,987 by Ayer and Theeuwes.

Wall 12 of osmotic dosage form 10 can be formed in one technique using the air suspension procedure. This procedure consists in suspending and tumbling the compressed drug-push core laminate in a current of air and wall forming composition until a wall is applied to the drug-push compartment. The air suspension procedure is well-suited for independently forming the wall. The air suspension procedure is described in U.S. Pat. No. 2,799,241; J. Am. Pharm. Assoc., Volume 48, pages 451 to 454, (1959); and ibid, Volume 49, pages 82 to 84, (196). Osmotic dosage forms can also be coated with a wall forming composition in a Wurster ® air suspension coater, using methylene dichloride-methanol cosolvent, 80:20, wt:wt, an ethanol-water, or acetone-water cosolvent, 95:5 wt:wt using 2.5 to 4% solids. The Aeromatic ® air suspension coater using a methylene dichloride-methanol cosolvent, 80:20 wt:wt, also can be used for applying the wall. Other wall forming techniques such as pan coating system, where wall forming compositions are deposited by successive spraying of the composition on the drug-push compartment, accompanied by tumbling in a rotating pan. Finally, the wall coated compartments are dried in a forced air over at 30°C. to 50°C. for up to a week to free dosage form 10 of solvent. Generally, the walls formed by these techniques have a thickness of 2 to 30 mils with a presently preferred thickness of 4 to 10 mils.

Dosage form 10 of the invention is manufactured by standard manufacturing techniques. For example, in one manufacture the beneficial drug and other ingredients comprising the drug layer facing the exit means are blended and pressed into a solid layer. The drug and other ingredients can be blended with a solvent and mixed into a solid or semisolid formed by conventional methods such a ball-milling, calendering, stirring or rollmilling and then pressed into a preselected shape. The layer possesses dimensions that correspond to the internal dimensions of the area the layer is to occupy in the dosage form and it

also possesses dimensions corresponding to the second layer for forming a contacting arrangement therewith. Next, the push layer, is placed in contact with the drug layer. The push layer is manufactured using techniques for providing the drug layer. The layering of the drug layer and the push layer can be fabricated by conventional press-layering techniques. Finally, the two layer compartment forming members are surrounded and coated with an outer wall. A passageway is laser, leached, or mechanically drilled through the wall to contact the drug layer, with the dosage form optically oriented automatically by the laser equipment for forming the passageway on the preselected surface when a laser is used for forming the passageway.

In another manufacture, the dosage form is manufactured by the wet granulation technique. In the wet granulation technique, for example, the drug and the ingredients comprising the drug layer are blended using an organic solvent, such as isopropyl alcohol-ethylene dichloride 80:20 v:v (volume:volume) as the granulation fluid. Other granulating fluid such as denatured alcohol 100% can be used for this purpose. The ingredients forming the drug layer are individually passed through a 40 mesh screen and then thoroughly blended in a mixer. Next, other ingredients comprising the drug layer are dissolved in a portion of the granulation fluid, such as the cosolvent described above. Then the latter prepared wet blend is slowly added to the drug blend with continual mixing in the blender. The granulating fluid is added until a wet blend is produced, which wet mass then is forced through a 20 mesh screen onto oven trays. The blend is dried for 18 to 24 hours at 30°C. to 50°C. The dry granules are sized then with a 20 mesh screen. Next, a lubricant is passed through an 80 mesh screen and added to the dry screen granule blend. The granulation is put into milling jars and mixed on a jar mill for 1 to 15 minutes. The push layer is made by the same wet granulation

techniques. The compositions are pressed into their individual layers in a Manesty ® press-layer press.

Another manufacturing process that can be used for providing the compartment-forming composition layers comprises blending the powered ingredients for each layer independently in a fluid bed granulator. After the powered ingredients are dry blended in the granulator, a granulating fluid, for example, poly(vinyl-pyrrolidone) in water, or in denatured alcohol, or in 95:5 ethyl alcohol /water, or in blends of ethanol and water is sprayed onto the powders. Optionally, the ingredients can be dissolved or suspended in the granulating fluid. The coated powders are then dried in a granulator. This process granulates all the ingredients present therein while adding the granulating fluid. After the granules are dried, a lubricant such as stearic acid or magnesium stearate is added to the granulator. The granules for each separate layer are pressed then in the manner described above.

The dosage form of the invention is manufactured in another manufacture by mixing a drug with composition forming ingredients and pressing the composition into a solid lamina possessing dimensions that correspond to the internal dimensions of the compartment. In another manufacture the drug and other drug composition-forming ingredients and a solvent are mixed into a solid, or a semisolid, by conventional methods such as ballmilling, calendering, stirring or rollmilling, and then pressed into a preselected layer forming shape. Next, a layer of a composition comprising an osmopolymer and an optional osmagent are placed in contact with the layer comprising the drug. The layering of the first layer comprising the drug and the second layer comprising the osmopolymer and optional osmagent composition can be accomplished by using a conventional layer press technique. The wall can be applied by molding, spraying or dipping the pressed bilayer's shapes into wall forming

materials. Another and presently preferred technique that can be used for applying the wall is the air suspension coating procedure. The procedure consists in suspending and tumbling the two layers in current of air until the wall forming composition surrounds the layers. The air suspension procedure is described in U.S. Pat. No. 2,799,241; J. Am. Pharm. Assoc., Vol. 48 pp 451-454 (1979); and, ibid, Vol. 49, pp 82-84 (1960). Other standard manufacturing procedures are described in Modern Plastics Encyclopedia, Vol 46, pp 62-70 (1969); and in Pharmaceutical Science, by Remington, 14th Ed., pp 1626-1678 (1970), published by Mack Publishing Co., Easton, Pa.

Exemplary solvents suitable for manufacturing the wall, the laminates and laminae include inert inorganic and organic solvents final laminated wall. The solvents broadly include members selected for the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cyclaliphatics, aromatics, heterocyclic solvents and mixtures thereof. Typical solvents include acetone, diacetone, alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptaene ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, carbon tetrachloride, chloroform, nitroethane, nitropropane, tetrachoroethan, ethyl ether, isopropyl ether, cyclohexane, cyclooctane, benzene, toluene, naphtha, tetrahydrofuran, diglyme, aqueous and nonaqueous mixtures thereof, such as acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, and ethylene dichloride and methanol.

DETAILED DISCLOSURE OF EXAMPLES OF THE INVENTION

The following examples are merely illustrative of the present invention and they should not be considered as limiting the scope of the invention in any way as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, the drawings and accompanying claims.

EXAMPLE 1

A dosage form adapted for delivering a drug in a therapeutic range is manufactured as follows: first a displacement or push layer is prepared by blending and passing through a stainless steel sizing screen having a mesh opening of 420 microns 587.5 grams of sodium carboxymethylcellulose having a degree of polymerization of approximately 3,200 and a degree of substitution of 0.7 carboxymethyl groups per anhydroglucose unit, 300 grams of powdered sodium chloride, 50 grams of hydroxypropylcellulose having a molecular weight of approximately 60,000 grams per mole, and 50 grams of hydroxypropylmethylcellulose having an average methoxyl content of 29 weight percent and an average hydroxypropyl content of 10 weight percent and an average molecular weight of approximately 11,300 grams per mole. Next 10 grams of red ferric oxide were passed through a sizing screen having openings of approximately 250 microns. The resulting powders were mixed in a planetary mixer to a uniform blend. The resulting blend was wet granulated by adding with stirring anhydrous ethyl alcohol until, a cohesive mass was formed. This mass was passed through a sizing screen having openings of approximately 840 microns, forming coated displacement particles, which were an dried overnight at ambient temperature and humidity. The dried particles were then passed again through the 840 micron sizing screen. Next 2.5 grams of

magnesium stearate, which had been previously sized through a mesh having 180 micron openings, were tumble mixed into the coated particles.

A composition comprising a drug of the structural formula was prepared as follows: first, a drug composition was prepared by passing 840 grams of venlafaxine hydrochloride, 100 grams of hydroxypropylcellulose having a molecular weight of approximately 60,000 grams per mole, and 50 grams of polyvinylpyrrolidone having a molecular weight of approximately 40,000 grams per mole, were passed through a sizing having openings of approximately 420 microns, and mixed in a planetary mixer to yield a uniform blend. Then, anhydrous ethyl alcohol was added to the mixture with stirring to produce a cohesive damp mass. The resulting damp mass was sized through a sieve having an opening of 840 microns, producing coated venlafaxine drug, which was air dried overnight. The resulting dried coated venlafaxine drug was passed again through the sizing screen having an 840 micron opening. Next, 10 grams of magnesium stearate, sized to 180 microns, was tumble mixed into the blend.

Next, the displacement-push composition and the drug composition were formed into a bilayer core as follows: first, 87 mg of the drug composition was placed in a 9/32 inch round die cavity and lightly tamped with a standard concave round tooling to form a slightly cohesive layer. Then, 70 mg of push composition was added to die and the and the resulting fill was compressed with a final force of 2 tons, thereby forming a two layer cores.

The bilayer cores were placed next in a coating pan having a 12 inch diameter and they were coated with a wall-forming solution. The wall-forming solution was prepared by dissolving 380 grams of cellulose

acetate having an acetyl content of 39.8 weight percent in 7,220 grams of acetone. In a separate mixing vessel, 20 grams of polyethylene glycol having a molecular weight of approximately 3,350 grams per mole were dissolved in approximately 380 grams of purified water. The two solutions were mixed to form the wall-coating solution which was spray coated onto the cores until about 20 mg of wall composition was deposited on the surfaces of the bilayer core.

A delivery exit port was formed across the wall by drilling an exit port, centered on the face of the dosage form on the drug composition side of the dosage form. The resulting dosage form was placed in simulated physiological fluid at 37°C., and the dosage form delivered a dose of 73 mg of venlafaxine hydrochloride at a controlled, zero rate over an extended duration of 15 hours.

EXAMPLE 2

The procedure of Example 1 was followed with the manufacturing procedures as set forth, except that the drug composition comprises 890 grams of venlafaxine hydrochloride, 100 grams of hydroxypropylcellulose, and 10 grams of magnesium stearate. The resulting dosage form released in simulated intestinal fluid 77 mg of venlafaxine hydrochloride at a zero-order rate over an extended duration of 16 hours.

EXAMPLE 3

The procedure of Example 1 was followed with all manufacturing steps as described, except that the drug composition consists of 650.0 grams of venlafaxine hydrochloride, 240.0 grams of maltodextrin having an average molecular weight of approximately 1800 grams per mole and an average degree of polymerization of 11.1, 80.0 grams of

hydroxypropyl cellulose, 20.0 grams of polyvinyl pyrrolidone, and 10.0 grams of magnesium stearate. The resulting dosage form was tested in artificial intestinal fluid, the dosage form delivered a dose of 57 mg of venlafaxine hydrochloride at zero order rate over a period of 15 hours.

EXAMPLE 4

The procedure of Example 1 was repeated with the manufacture as previously set-forth, except that the drug composition consists of 840.0 grams of venlafaxine hydrochloride, 150.0 grams of polyethylene oxide having an average molecular weight of approximately 100,000 grams per mole, and 10.0 grams of magnesium stearate. The wall weight weighed approximately 25 mg. The resulting dosage forms were tested in simulated intestinal fluid, and they released a dose of 73 mg of venlafaxine hydrochloride at controlled rate over an extended period of 20 hours.

EXAMPLE 5

The compositions were manufactured as in Example 1. The process of manufacture was the same except that the push layer manufactured was prepared in a fluid bed aqueous-based granulation process. This was accomplished by sizing the sodium carboxymethyl cellulose, the sodium chloride, the hydroxypropyl cellulose, and red ferric oxide through a screen having openings of 420 microns. The resulting powders were charged into a fluid bed granulation column and binder solution consisting of the hydroxypropyl methylcellulose at a 5 percent solids concentration in water was sprayed on, thereby forming the granules for the push layer.

EXAMPLE 6

The compositions and processes followed in this example were the same as in Example 1 except the push consisted of 740.0 grams polyethylene oxide with an average molecular weight of approximately 5 million grams per mole, 200.0 grams of sodium chloride, 50.0 grams of hydroxypropyl methyl cellulose having average molecular weight of approximately 11,300 per mole, 5.0 grams of red ferric oxide, and 5.0 grams of magnesium stearate.

DESCRIPTION OF METHOD OF PERFORMING THE INVENTION

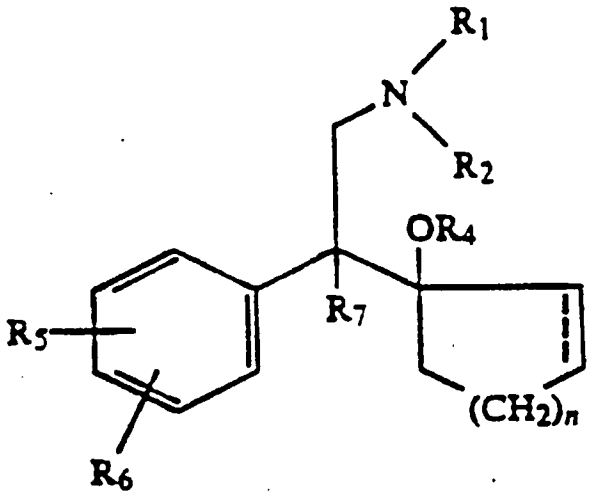
Additional embodiments of the invention pertains to a method for delivering a drug embraced by the structural formula of this invention for its intended therapy. One embodiment pertains to a method for delivering a drug of the formula by administering a dosage form comprising 0.5 mg to 750 mg of the drug from a dosage form selected from sustained-release and controlled-release dosage forms in a therapeutically responsive dose over an extended period of time. Another embodiment of the invention pertains to a method for delivering a drug of the formula disclosed in this invention, to the gastrointestinal tract of a human in need of this therapy, wherein the method comprises the steps of: (A) admitting orally into the gastrointestinal tract of the human a dosage form comprising: (1) a non-toxic wall composition comprising means for imbibing an external aqueous fluid through the wall into the dosage form, which wall surrounds and defines; (2) an internal compartment; (3) a drug composition comprising a drug of the formula in the compartment comprising a dosage unit amount of said drug; (4) a push composition in the compartment for pushing the drug composition from the compartment; (5) at least one exit means in the wall for delivering the drug from the dosage form; (B) imbibing fluid through the wall into the

compartment thereby causing the composition to form a deliverable dosage form and concomitantly causing the push composition to expand and push the drug composition through the exit means from the dosage form; and (C) deliver the therapeutic drug in a therapeutically effective amount at a controlled rate over an extended period of time to the patient in need of said therapy. The method also comprising dispensing a dose amount of said drug from an instant release exterior dosage amount of drug to the patient for providing instant anti-depressant therapy.

Inasmuch as the foregoing specification comprises preferred embodiments of the invention, it is understood that variations and modifications may be made herein, in accordance with the inventive principles disclosed, without departing from the scope of the invention.

We claim:

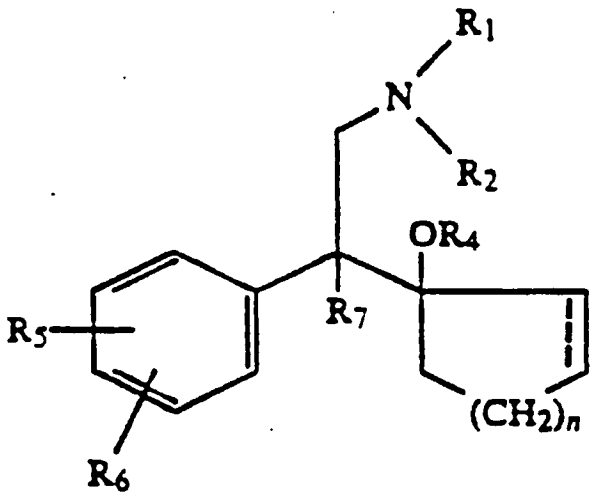
1. A therapeutic composition comprising 0.5 mg to 750 mg of a drug of the formula:



wherein the dotted line represents an unsaturation or a cycloalkenyl group; R_1 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_2 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_4 is a member selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms, formyl, and alkanoyl of 2 to 7 carbon atoms; R_5 and R_6 are independently a member selected from the group consisting of hydrogen, hydroxyl, an alkyl of 1 to 6 carbon atoms, an alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms in which each alkyl group comprises 1 to 6 carbon atoms, alkanamide of 2 to 7 carbon atoms, halo, and trifluoroethyl, R_7 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbons, and n is one of the integers 0, 1, 2, 3, and 4, and a pharmaceutically acceptable addition

salt; and wherein the drug of the formula is blended with a poly(alkylene oxide) polymer.

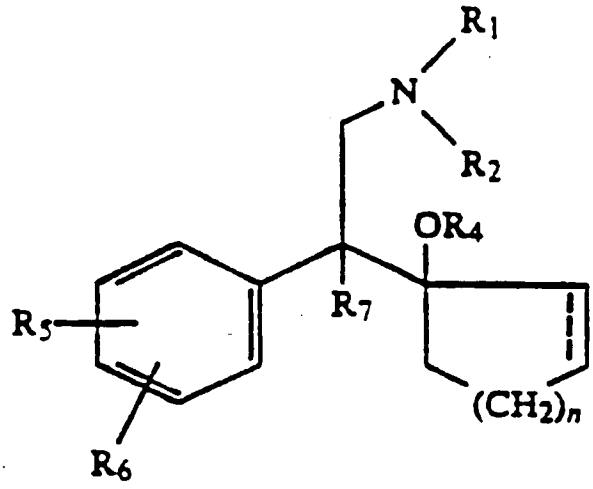
2. A therapeutic composition comprising 0.5 mg to 750 mg of a drug of the formula;



wherein the dotted line represents an unsaturation or a cycloalkenyl group; R_1 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_2 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_4 is a member selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms, formyl, and alkanoyl of 2 to 7 carbon atoms; R_5 and R_6 are independently a member selected from the group consisting of hydrogen, hydroxyl, an alkyl of 1 to 6 carbon atoms, an alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms in which each alkyl group comprises 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, and trifluoroethyl; R_7 is a member selected from the group

consisting of hydrogen and alkyl of 1 to 6 carbons and n is one of the integers 0, 1, 2, 3, 4, and a pharmaceutically acceptable addition salt; and wherein the drug of the formula is blended with a cellulose polymer.

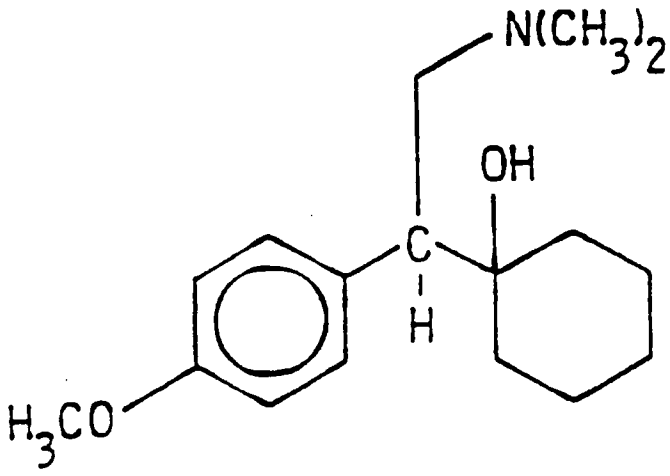
3. A therapeutic composition comprising 0.5 mg to 750 mg of a drug of the formula:



wherein the dotted line represents an unsaturation or a cycloalkenyl group; R_1 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_2 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_4 is a member selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms, formyl, and alkanoyl of 2 to 7 carbon atoms; R_5 and R_6 are independently a member selected from the group consisting of hydrogen, hydroxyl, an alkyl of 1 to 6 carbon atoms, an alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, nitro, alkylmercapto of 1 to 6

carbon atoms, amino, alkylamino of 1 to 6 carbon atoms in which each alkyl group comprises 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, and trifluoroethyl, R_7 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbons, and n is one of the integers 0, 1, 2, 3, and 4; and a pharmaceutically acceptable addition salt; and wherein the drug of the formula is blended with a maltodextrin polymer.

4. A dosage form for administering a drug to an environment of use, wherein the dosage form comprises a drug of the formula:



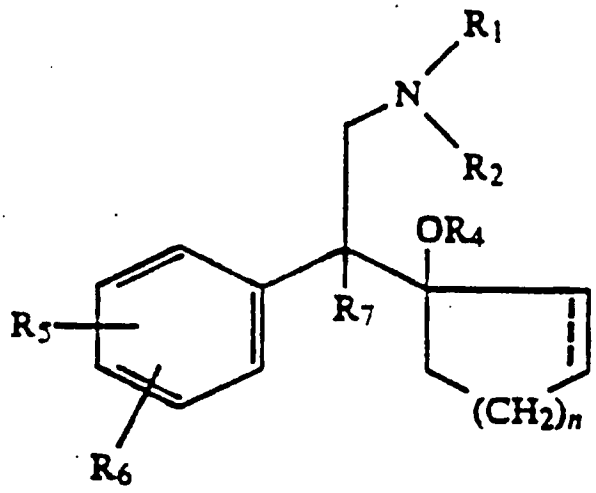
which dosage form comprises a member selected from the group consisting of a sustained-release dosage form and a controlled release dosage form, and wherein said dosage form comprises means for storing the drug and means for releasing the drug over an extended period of time.

5. A dosage form for the oral delivery of a drug to an environment of use, wherein the dosage form comprises:

(a) a wall comprising at least in part a composition permeable to the passage of fluid, which wall surrounds:

(b) a compartment;

(c) a drug composition in the compartment comprising a drug of the formula:



wherein the dotted line represents a member selected from the group consisting of an unsaturation and cycloalkenyl group; R_1 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_2 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms; R_4 is a member selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms, formyl, and alkanoyl of 2 to 7 carbon atoms; R_5 and R_6 are independently a member selected from the group consisting of hydrogen, hydroxyl and alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alknaoyloxy of 2 to 7 carbon atoms, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo and trifluoroethyl; R_7 is a member selected from the group consisting of hydrogen and alkyl of 1 to 6 carbons; an n is 0 to 4; and

(d) a displacement in the compartment comprising a composition comprising an osmotically active compound; and,

(e) an exit passageway in the dosage form for delivering the drug composition from the dosage form.

6. A dosage form for the oral delivery of the drug to an environment of use according to claim 5, wherein the drug is 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol.

FIG.1

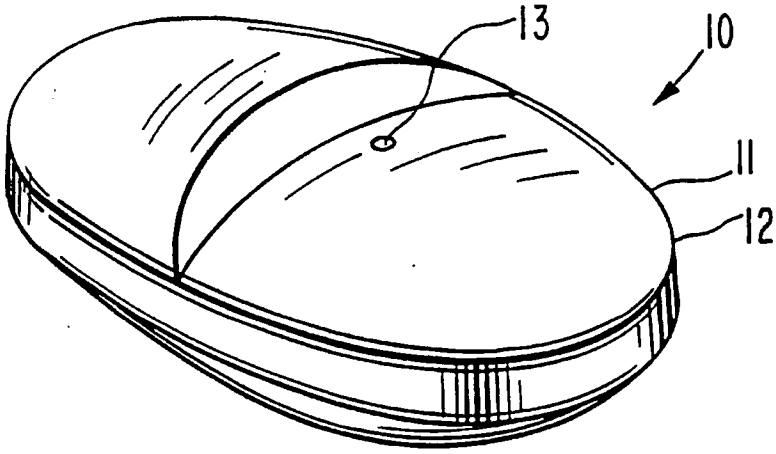


FIG.2

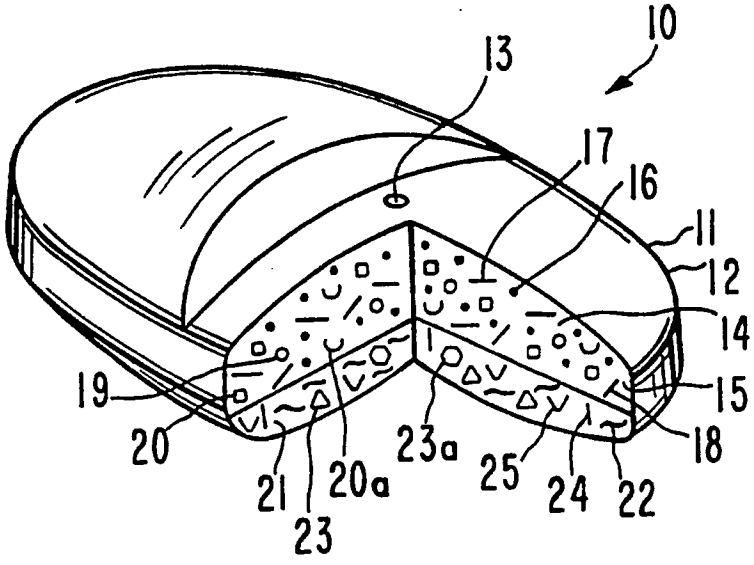


FIG.3

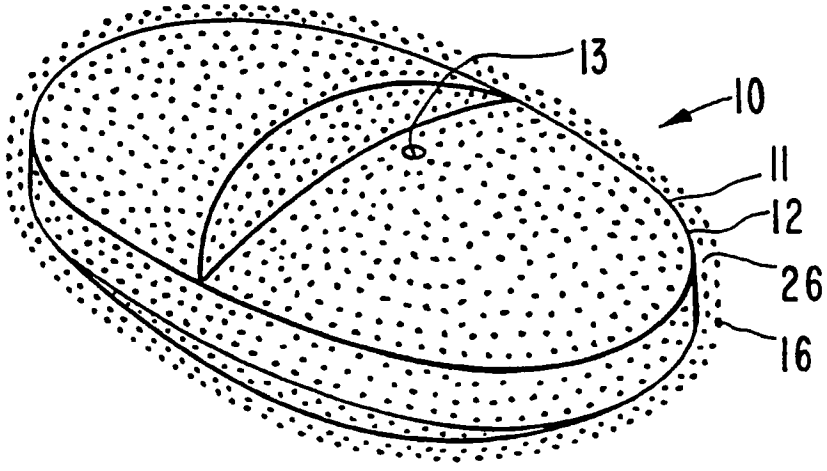


EXHIBIT 6

ENTIRE EXHIBIT UNDER SEAL

EXHIBIT 7

HellerEhrman LLP

October 30, 2006

Via Facsimile

Samuel F. Ernst
Sam.Ernst@HellerEhrman.com
Direct +1.415.772.6964
Direct Fax +1.415.772.1759
Main +1.415.772.6000
Fax +1.415.772.6268

40443.0005

Linda A. Wadler
Finnegan Henderson Farabow Garrett
& Dunner LLP
901 New York Ave., NW
Washington, D.C. 20001-4413

Re: *Wyeth v. Impax Laboratories, Inc.*, No. 06-222 JF

Dear Linda:

We write to raise deficiencies in Wyeth's Supplemental Responses to Impax's First Set of Interragotories and Wyeth's Responses to Impax's Second Sets of Interrogatories. Please advise us if Wyeth will serve supplemental responses to correct the deficiencies raised below. In light of the fact that the deadline for completion of contention interrogatories was October 10, we request that Wyeth supplement its responses by November 6, 2006.

- **Interrogatory No. 6**: Wyeth has failed to provide a substantive response to this contention interrogatory, which seeks Wyeth's position on claim construction, and Wyeth has failed to supplement its response by the October 10 deadline. Any reliance on the Scheduling Order setting a date for exchange of claim terms is misplaced. That date is a final exchange of the claim terms so that the party's can submit their Markman briefs approximately three weeks later. It was not meant to preclude answers to contention interrogatories also specified in the Court's Scheduling Order. As the patentee, Wyeth must have a position regarding the proper interpretation of the claims it has asserted. This is the first step in an infringement analysis that Wyeth should have performed pursuant to Federal Rule of Civil Procedure 11 before filing this suit. Moreover, Wyeth previously has asserted constructions of the same claims of the patents-in-suit in the Teva litigation, and thus has already performed an analysis of the claims in that case. Finally, Wyeth has had Impax's ANDA, which sets forth Impax's formulation, since August 7, 2006; thus, Wyeth cannot delay responding on the ground that it needs discovery of the accused product. In sum, Wyeth must set forth its construction of terms of the asserted claims, along with any intrinsic or extrinsic evidence in support of each of these constructions. Impax has provided a complete answer to Wyeth's Interrogatory 5 concerning claim construction and there is no justification for Wyeth's refusal to answer Impax's interrogatory on the same topic.

- **Interrogatory No. 9**: In response to this interrogatory, Wyeth states that it "reserves the right to correct, clarify, or supplement its response to these interrogatories by, for example, asserting additional claims." Wyeth may not assert additional claims now that the October 10 deadline for completion of contention interrogatories has passed. Moreover, Wyeth has represented to Impax during meet and confer that it would not assert additional claims, and Impax is preparing its defense and has prepared its discovery responses in reliance upon this representation. Please amend Wyeth's response to this interrogatory to omit the unfounded statement that "Wyeth reserves the right to correct, clarify, or supplement its response to these interrogatories by, for example, asserting additional claims."

Wyeth further states in response to this interrogatory that "in its Notice Letter, Impax did not challenge infringement with respect to any of the limitations in any of claims 20-25 of the '171 patent other than 'extended release formulation' and that, therefore, at least with respect to all of the other limitations in those claims, Impax has admitted literal infringement." Impax has made no such admission. Please identify your authority for the proposition that a party waives all theories of non-infringement not specifically articulated in its Notice Letter. To the extent Wyeth's contentions are based on this erroneous view of the law, they are inadequate and must be amended.

- **Interrogatory No. 10**: Wyeth has failed to supplement its response to this interrogatory by the October 10 deadline. Wyeth identified the entire patent specification of the patents-in-suit in its initial response to this contention interrogatory, which seeks Wyeth's position as to the written description that supports the asserted claims. It is neither credible nor consistent with the rules of discovery for Wyeth to maintain that every word in a given patent provides the written description for every claim in that patent. If such is the case, then Wyeth should be precluded from specifying otherwise in any briefing regarding the adequacy of the written description for a particular asserted claim.

- **Interrogatory No. 17**: Wyeth invokes Federal Rule of Civil Procedure 33(d) in response to this interrogatory but fails to specify the documents from its document productions wherein the requested information may be found. Wyeth should supplement its response to this interrogatory "in sufficient detail to permit the interrogating party to locate and to identify, as readily as can the party served, the records from which the answer may be ascertained." Fed. R. Civ. P. 33(d).

- **Interrogatories Nos. 26-27**: Wyeth has failed to respond to this interrogatory, which seeks Wyeth's contentions regarding which limitations are not disclosed in specific prior art references. There is no basis for Wyeth's objection that Impax bears the burden of proof on invalidity. We are aware of no authority that relieves a party of its discovery obligations merely because it does not bear the burden of proof on a particular issue. Impax has fully responded to Wyeth's contention interrogatories on issues on which Wyeth bears the

burden of proof, such as, for example, infringement. Please advise us whether and when Wyeth will supplement its answer to this interrogatory.

- **Interrogatory No. 28**: Wyeth states in response to this interrogatory that "Impax made no allegations that the asserted claims of the patents-in-suit were either unenforceable or invalid in its Patent Certification Notice, as it was required to do if it had any basis for asserting invalidity or unenforceability of those claims." Impax's notice explicitly reserved its right to assert invalidity, unenforceability, and other grounds of non-infringement. Please provide us with your authority for the proposition that a party may not allege invalidity or unenforceability in defense of a lawsuit for patent infringement because it did not state these theories with particularity in its Patent Certification Notice. We are aware of no such authority, and to the extent Wyeth's response is based on this erroneous legal understanding, Wyeth must supplement its response to this interrogatory.

- **Interrogatory No. 34**: This interrogatory asks Wyeth to *identify* all relationships, agreements, pacts, engagements, or understandings between Wyeth and Alza concerning Alza's research and development of an extended release venlafaxine capsule. Instead, Wyeth has invoked Rule 33(d) without specifying which documents contain the information sought. Please advise us whether and when Wyeth will supplement this interrogatory to respond "in sufficient detail to permit the interrogating party to locate and to identify, as readily as can the party served, the records from which the answer may be ascertained." Fed. R. Civ. P. 33(d).

- **Interrogatory No. 35**: Wyeth has failed to respond to this interrogatory. In its response to this interrogatory, Wyeth was required to set forth whether it contends that the named inventors never had knowledge of Alza's development of a venlafaxine extended release product beyond the Alza patent publication cited in the patents-in-suit, or whether such knowledge was not material to patentability, and the bases therefore. This interrogatory seeks information that is in the possession of Wyeth and has been for some time. Please advise us whether and when Wyeth will supplement its response to this interrogatory.

- **Interrogatory No. 36**: This interrogatory seeks all factual and legal bases for Wyeth's contention that the quoted passage was not material to patentability and was not made with intent to deceive the PTO. In response, Wyeth has incorporated its response to Interrogatory No. 37, which is an interrogatory on the issue of obviousness in light of Wyeth's Inderal LA (propranolol HCl) Long-Acting Capsules. Accordingly, the response to Interrogatory No. 36 is non-responsive. Please advise us whether and when Wyeth will supplement its response to this interrogatory.

Enclosed herein, please find Impax's verifications of its recently served discovery responses.

Best regards,

Samuel F. Ernst

Enclosure

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Facsimile Transmittal

HellerEhrman LLP
333 Bush Street
San Francisco, CA 94104-2878
Main: +1.415.772.6000
Fax: +1.415.772.6268

To: Linda A. Wadler, Esq., Finnegan Henderson, et al., Washington, D.C.
Telephone: 1.202.408.4000 **Fax:** 1.202.408.4400

From: Samuel F. Ernst
Telephone: +1.415.772.6964

No. of Pages: 6 (including cover)
Date: October 30, 2006

40443.0005 (8004)

Message:

SF 1290979 v1
10/30/06 9:49 AM (40443.0005)

EXHIBIT 8

HellerEhrman LLP

November 27, 2006

Via Facsimile

Samuel F. Ernst
Sam.Ernst@HellerEhrman.com
Direct +1.415.772.6964
Direct Fax +1.415.772.1759
Main +1.415.772.6000
Fax +1.415.772.6268

40443.0005

Linda A. Wadler
Finnegan Henderson Farabow Garrett
& Dunner LLP
901 New York Ave., NW
Washington, D.C. 20001-4413

Re: *Wyeth v. Impax Laboratories, Inc.*, No. 06-222 JF

Dear Linda:

This letter is to follow up on the issues we discussed during our meet and confer of November 20, 2006 regarding Wyeth's responses to Impax's interrogatories.

You said that you would get back to us with a date by which Wyeth will supplement those responses that it has agreed to supplement. We requested that Wyeth supplement at the beginning of December.

Wyeth has agreed to supplement its response to Impax's Interrogatory No. 6.

Regarding Interrogatory Nos. 9 and 28, we acknowledged that the parties disagree as to whether 21 U.S.C. § 355(j)(2)(B)(iv)(II) or 21 C.F.R. § 314.95(c)(6) operate to preclude Impax from relying on legal theories not specified in its ANDA. Impax's position is that this disagreement need have no bearing on this meet and confer, so long as Wyeth will verify that it is not withholding information in response to Impax's interrogatories on the basis of its interpretation of these provisions. You said that you would verify this for us and get back to us shortly.

Wyeth agrees to supplement its response to Interrogatory No. 10 by providing its contention as to the written description support for the claim term "extended release formulation."

Regarding Interrogatory Nos. 17 and 34, Impax's position is that in invoking Rule 33(d), Wyeth must specify the documents that contain the answer to the interrogatory in question by citation to Bates number. The parties may supplement their responses to interrogatories in which they invoke Rule 33(d) to the extent they later learn of additional

documents containing the answer to the interrogatory, but it is insufficient to specify no documents whatsoever in relying on Rule 33(d). Both parties agreed to review their responses in which they invoked Rule 33(d) to determine if supplementation is required.

Wyeth will supplement its response to Interrogatory No. 26 only with regard to WO 94/27589. Wyeth will not supplement its response to this interrogatory to state which limitations of the asserted patent claims it contends are absent from the other five prior art references listed in the interrogatory. However, Wyeth will supplement its answer to Interrogatory No. 27, which also seeks contentions regarding the same prior art references. We will review Wyeth's supplemental answer to Interrogatory No. 27 and to the extent it does not contain Wyeth's contentions with regard to which limitations of the asserted claims are lacking in each of the listed prior art references, we will consider moving to compel a further response to Interrogatory No. 26.

Wyeth will not supplement its response to Interrogatory No. 35. Wyeth disagrees with Impax that this interrogatory requests information germane to Impax's unenforceability and invalidity defenses and that Impax is therefore entitled to discover this information under Rule 26. As a compromise, we requested that Wyeth respond to this interrogatory by answering the following question: "Does Wyeth contend that the named inventors of the patents-in-suit were unaware of Alza's development of an extended release formulation comprising venlafaxine beyond the disclosure in publication WO 94/27589?" If Wyeth will agree to respond to this interrogatory by providing this information, we will not move to compel an answer to this interrogatory.

Please let me know if you have a different understanding as to my characterization of any of these issues.

Best regards,

Samuel F. Ernst

11/27/2006 10:07 FAX 001

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*** TX REPORT ***
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RESULT	OK

Facsimile Transmittal

HellerEhrman LLP
333 Bush Street
San Francisco, CA 94104-2878
Main: +1.415.772.6000
Fax: +1.415.772.6268

To: Linda A. Wadler, Esq., Finnegan Henderson, et al., Washington, D.C.
Telephone: 1.202.408.4000 **Fax:** 1.202.408.4400

From: Samuel F. Ernst
Telephone: +1.415.772.6964

No. of Pages: 3 (including cover)
Date: November 27, 2006

40443.0005 (8004)

Message:

SF 1290979 v1
11/27/06 8:45 AM (40443.0005)

EXHIBIT 9

FINNEGAN HENDERSON FARABOW GARRETT & DUNNER LLP

901 New York Avenue, NW ▪ Washington, DC 20001-4413 ▪ 202.408.4000 ▪ Fax 202.408.4400
www.finnegan.com

BARBARA R. RUDOLPH
202.408.4346
barbara.rudolph@finnegan.com

December 4, 2006

Samuel F. Ernst, Esq.
Heller Ehrman LLP
333 Bush Street
San Francisco, CA 94140-2878

VIA FACSIMILE

Wyeth v. Impax Laboratories, Inc., Civil Action No.: 06-222 (D. Del.)

Dear Samuel:

We are writing in response to your letter of November 27, 2006 to Linda Wadler pertaining to the issues we discussed during the November 20, 2006 meet and confer telephone conference regarding Wyeth's Responses to Impax's Interrogatories. We provide our responses below.

Wyeth's Supplemental Interrogatory Responses

We agree to provide the supplemental interrogatory responses that are outlined in our letter of November 17, 2006 by ***December 20, 2006***.

Wyeth's Response to Interrogatory No. 6

Wyeth has agreed, as set forth in our November 17th letter, to supplement its response to Interrogatory No. 6.

Wyeth's Supplemental Response to Interrogatory No. 9 and Response to Interrogatory No. 28

Wyeth still maintains that, under 21 U.S.C. § 355(j)(2)(B)(iv)(II) and 21 C.F.R. § 314.95(c)(6), Impax was required to fully set forth its grounds for non-infringement, invalidity, and unenforceability in its Notice Letter. We confirm, however, that Wyeth did not withhold information in response to Interrogatory Nos. 9 and 28 on the basis of our interpretation of these provisions. Wyeth reserves its right to supplement its responses in the event that additional issues are raised.

Wyeth's Response to Interrogatory No. 10

As discussed in our November 17th letter, Wyeth agrees to supplement Interrogatory No. 10 to provide specific portions of the patent specification, in addition to the specification as a whole, that provides written description support for the claim term "extended release formulation."

Wyeth's Supplemental Response to Interrogatory No. 17 and Response to Interrogatory No. 34

Wyeth maintains its objections to these interrogatories, and maintains that, in light of those objections, its response was entirely appropriate. With respect to Interrogatory No. 17, however, we referred Impax, in our November 17th letter, to Wyeth's expert reports from the prior *Teva* litigation which include discussion of the evidence of secondary considerations and citations to documents upon which Wyeth has relied in the past, and would rely upon in this litigation. As we noted in our November 17th letter, Impax has no basis to complain about Wyeth's response, in light of Wyeth's detailed supplemental response to Interrogatory No. 17, and the extensive expert reports that have been provided to Impax which identify voluminous objective evidence of non-obviousness. In an effort to compromise, however, Wyeth agrees to supplement Interrogatory No. 17 to incorporate its reliance on its expert reports.

As to Interrogatory No. 34, Impax still has not articulated any nexus between the information sought and any claim or defense in this litigation. Unless and until Impax can provide Wyeth with any such nexus, we see no reason to supplement Wyeth's response to this interrogatory.

Wyeth further reserves the right to supplement its responses to these interrogatories as discovery in this case develops.

Wyeth's Responses to Interrogatory Nos. 26-27

As you have noted in your November 27th letter, Wyeth agrees to supplement its Response to Interrogatory No. 26, but only with respect to Impax's allegation that WO 94/27589 "inherently anticipates" claims 1 through 6 of U.S. Patent No. 6,419,958 and claim 1 of U.S. Patent No. 6,403,120. Wyeth maintains its objections to any further supplementation of Interrogatory No. 26. Wyeth agrees, as discussed in our November 17th letter, to supplement its Response to Interrogatory No. 27.

Wyeth's Response to Interrogatory No. 35

We appreciate your effort to resolve this issue by proposing an alternate question instead of pressing for a response to Interrogatory No. 35 as originally drafted. However, we note that at this time, based upon Impax's contentions as outlined in its First Amended Responses to Plaintiff's First Set of Interrogatories, Wyeth has no need

to formulate any contentions with respect to the specific question posed. The question posed in your November 27th letter is not relevant to any issue in this case. Wyeth, therefore, declines to answer your proposed question.

We hope that these matters can now be considered resolved. As always, however, we are happy to further discuss any of the issues discussed above at your convenience.

Sincerely,

Barbara R. Rudolph

cc: Mary B. Matterer, Esq. (via Facsimile)
Richard K. Herrmann, Esq. (via Facsimile)

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
901 New York Avenue, NW
Washington, DC 20001-4413

Telephone
(202) 408-4000

Facsimile
(202) 408-4400

FACSIMILE TRANSMITTAL

TO		FROM	
Name:	Mary B. Matterer, Esq.	**Name:**	Barbara Rudolph
Firm:	Morris James Hitchens & Williams LLP	**Phone No.:**	(202) 408-4346
Fax No.:	(302) 571-1750	**Fax # Verified by:**	J. La Follette
Phone No.:	(302) 888-6800	**# Pages (incl. this):**	4
Date:	December 4, 2006	**Our File No.:**	
Subject:	*Wyeth v. Impax*		

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EXHIBIT 10

HellerEhrman LLP

January 29, 2007

Via Facsimile

Samuel F. Ernst
Sam.Ernst@HellerEhrman.com
Direct +1.415.772.6964
Direct Fax +1.415.772.1759
Main +1.415.772.6000
Fax +1.415.772.6268

40443.0005

Robert A. Pollock, Esq.
Finnegan, Henderson, Farabow,
Garrett & Dunner, L.L.P.
901 New York Ave., NW
Washington, DC 20001

Dear Robert:

This letter is in regard to Wyeth's Supplemental Responses to Impax's Interrogatories, served on January 12.

Interrogatory No. 11

Wyeth has responded to the first part of this interrogatory, asking it to identify opinions of counsel, by stating that it will identify protected documents on a withheld document list. We understand this to mean that Wyeth is asserting attorney-client privilege with regard to all such documents.

This interrogatory also asks Wyeth to "IDENTIFY any search of prior art conducted by WYETH or on WYETH's behalf." Rather than identifying prior art searches, Wyeth states that it incorporates by reference the objections and response to interrogatory No. 5. But Wyeth's response to Interrogatory No. 5 merely lists prior art references – it does not identify prior art searches. Is Wyeth asserting attorney-client privilege with regard to all prior art searches that it conducted or that were conducted on Wyeth's behalf? If not, we would request that Wyeth identify all prior art searches.

Interrogatory No. 18

Wyeth has supplemented its response to this interrogatory by referring Impax to the organizational charts at Bates Nos. WYETH168-0000001 through 000034. But these organizational charts are only for the years 1991 through 1996. We would request information regarding Wyeth's organizational structure during at least the period of time that the patents-in-suit were in prosecution.

The interrogatory asks Wyeth to identify not only its internal organizational structure, but also to identify its corporate structure – its parents, subsidiaries, affiliates, etc. We would ask Wyeth to provide this information in response to the interrogatory.

Interrogatory Nos. 34 and 35

We strongly disagree with Wyeth's refusal to respond to these interrogatories. The agreements Wyeth had with Alza and the persons at Wyeth aware of the Alza prior art are relevant to Impax's invalidity defense based on the Alza prior art. Because the parties' dispute on this topic was extensively discussed during meet and confer, we ask that Wyeth reconsider its refusal to respond to these interrogatories and reply to this letter by this Friday, February 2, or we will be forced to move to compel.

Sincerely,

Samuel F. Ernst

EXHIBIT 11

FINNEGAN HENDERSON FARABOW GARRETT & DUNNER LLP

901 New York Avenue, NW ▪ Washington, DC 20001-4413 ▪ 202.408.4000 ▪ Fax 202.408.4400
www.finnegan.com

ROBERT A. POLLOCK
202.408.4081
robert.pollock@finnegan.com

February 2, 2007

VIA FACSIMILE

Samuel F. Ernst, Esq.
Heller Ehrman LLP
333 Bush Street
San Francisco, CA 94140-2878

Wyeth v. Impax Laboratories, Inc., Civil Action No.: 06-222 (D. Del.)

Dear Samuel:

Thank you for your letter of January 29, 2007 regarding Wyeth's Supplemental Responses to Impax Interrogatory Nos. 11, 18, 34, and 35. We respond to the points raised in that letter below.

Interrogatory No. 11

We confirm that Wyeth asserts the attorney-client privilege and/or work product immunity for any otherwise responsive opinion of counsel relating to "patentability, novelty, validity, invalidity, state of the art, enforceability, scope, or infringement," as recited in part (a) of Impax Interrogatory No. 11.

Part (b) of Impax Interrogatory No. 11 requests the identity of "any search of prior art conducted by WYETH or on WYETH's behalf." Wyeth responded, subject to its stated objections, by incorporating its response to Interrogatory No. 5. We confirm that Wyeth asserts the attorney-client privilege and/or work product immunity for any "search of the prior art" conducted by or at the behest of Wyeth's counsel and/or in preparation for litigation.

Because the term "prior art" calls for a legal conclusion, by definition, "prior art searches" are privileged and/or work product immune by nature. Therefore, the existence of any such search, to the extent it was conducted prior to February 2003, will be noted on Wyeth's privilege log. Any references, patents, or publications identified as a result of any prior art search, however, are included in the list of art cited in response

to Interrogatory No. 5. Therefore, our incorporation of our response to Interrogatory No. 5 was entirely appropriate.

Finally, please note that any non-privileged/work product immune literature searches were not withheld from production to Impax.

Interrogatory No. 18

As part of its response to this interrogatory, Wyeth has identified organization charts of Wyeth's Pharmaceutical Sciences Division for the years 1991 through 1996. This information encompasses the positions of the named inventors, their coworkers, and supervisors at the time the patents in suit were filed. Impax's blanket request for information regarding Wyeth's organizational structure after 1996 is overly broad and irrelevant. Wyeth will nevertheless reconsider its response if Impax can narrow its request to a particular division or department, and explain how such information is relevant to any issue in this case.

With respect to corporate structure, Wyeth has identified its former name of American Home Products Corporation, and identified Wyeth Pharmaceuticals as the division of Wyeth currently involved in the research, design, development, manufacture, operation, sales and marketing of the inventions of the patents in suit and the Effexor® XR products. We are therefore surprised by your request for additional information regarding Wyeth's "parents, subsidiaries, affiliates, etc." Such information is not only irrelevant to any issue in this case, but is readily available through public sources, including Wyeth's web site.

Interrogatory No. 34

Subject to its objections, Wyeth will supplement its response to Interrogatory No. 34 by identifying responsive documents pursuant to Fed. R. Civ. P. 33(d).

Interrogatory No. 35

Wyeth maintains that it has no obligation to respond to this interrogatory because Impax has not set forth allegations or contentions regarding inequitable conduct on the basis of "ALZA's development of an EXTENDED RELEASE FORMULATION comprising VENLAFAXINE." Nevertheless, in light of your November 27, 2006 letter proposing a compromise to Interrogatory No. 35 as originally drafted, Wyeth will agree to respond to the following question: "Does Wyeth contend that as of March 25, 1996, the named inventors were unaware that Alza was attempting to formulate a formulation comprising venlafaxine hydrochloride?" Please let us know if Impax agrees to this compromise.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

We hope that this resolves all outstanding issues raised in your letter of January 29th. Please let us know whether you would like to further discuss any of the matters addressed above.

Sincerely,

Robert A. Pollock

cc: Mary B. Matterer, Esq. (via facsimile)

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
901 New York Ave., NW
Washington, DC 20001

Telephone
(202) 408-4000

Facsimile
(202) 408-4400

FACSIMILE TRANSMITTAL

TO		FROM	
Name:	Samuel Ernst, Esq.	Name:	Robert A. Pollock, Esq.
Firm:	Heller Ehrman LLP	Phone No.:	(202) 408-4081
Fax No.:	415-772-6268	Fax # Verified by:	K. Danna - MD 832
Phone No.:	415-772-6964	# Pages (incl. this):	4
Subject:	Wyeth v. Impax	Date:	February 2, 2007
		Our File No.:	

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EXHIBIT 12

HellerEhrman LLP

February 5, 2007

Via E-mail

Samuel F. Ernst
Sam.Ernst@HellerEhrman.com
Direct +1.415.772.6964
Direct Fax +1.415.772.1759
Main +1.415.772.6000
Fax +1.415.772.6268

38508.0001

Robert A. Pollock, Esq.
Finnegan, Henderson, Farabow,
Garrett & Dunner, L.L.P.
901 New York Ave., NW
Washington, DC 20001

Re: *Wyeth v. ImpaxLaboratories, Inc.*, No. 06-222 (D. Del.)

Dear Robert:

This is in response to your letter of February 2, 2007 regarding Impax's Interrogatory Nos. 34 and 35. We are considering your response regarding Interrogatories 11 and 18 and will address those in a separate letter.

Thank you for agreeing to supplement Wyeth's response to Interrogatory No. 34. Please advise us of when Wyeth will be able to serve its supplemental response.

Regarding Interrogatory 35, we do not accept your proposal that Wyeth's obligation to answer this interrogatory be satisfied by answering the narrower question: "Does Wyeth contend that as of March 25, 1996, the named inventors were unaware that Alza was attempting to formulate a formulation comprising venlafaxine hydrochloride?" The compromise I had offered months ago on November 27, 2006 was not this question, but rather, the question, "Does Wyeth contend that the named inventors of the patents-in-suit were unaware of Alza's development of an extended release formulation comprising venlafaxine beyond the disclosure in publication WO 94/27589?" There was no date restriction. Whether the inventors were aware of the Alza research at any time – including throughout the entire period of the prosecution of the patents-in-suit – is relevant to Impax identifying witnesses in connection with its invalidity defense and to inequitable conduct. Accordingly, we cannot accept your date limitation.

We request that Wyeth respond to Interrogatory 35 in full. In light of impending deadlines, please let us know if Wyeth will respond to Interrogatory 35 by the close of business today.

Best regards,

Samuel F. Ernst

EXHIBIT 13

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

901 New York Avenue, NW ▪ Washington, DC 20001-4413 ▪ 202.408.4000 ▪ Fax 202.408.4400
www.finnegan.com

BARBARA R. RUDOLPH
202.408.4346
barbara.rudolph@finnegan.com

February 5, 2007

VIA FACSIMILE

Daniel N. Kassabian, Esq.
Heller Ehrman LLP
333 Bush Street
San Francisco, CA 94104

Wyeth v. Impax Laboratories, Inc., Civil Action No.: 06-222 (D. Del.)

Dear Daniel:

I am writing in response to your letter of February 2, 2007, regarding the deposition of Mark Shaw and Impax's Rule 30(b)(6) deposition and as a follow-up to our telephone conference earlier today.

First, during today's telephone conference, the parties agreed to taking the deposition of Impax's witnesses at Heller Ehrman's offices in San Francisco, and taking the deposition of Wyeth's witnesses at Finnegan's offices in Washington D.C. Impax will get back to us shortly about Mr. Shaw's availability for deposition in San Francisco next Wednesday, February 14th or later that week.

Further, with respect to Paragraph 3(d) of the Court's Rule 16 Scheduling Order, the parties agreed during the telephone conference that neither Wyeth nor Impax may assert that the commencement of depositions precludes further written discovery under Paragraphs 3(a)-(c).

As to Impax's Amended Rule 30(b)(6) Notice, we indicated our intent to file a motion for protective order, since we have not been able to reach agreement on many of the Topics in Impax's Amended Notice. You raised the question of whether we would be willing to proceed with the Rule 30(b)(6) deposition, prior to the final resolution of our motion for protective order, with respect to the narrowed topics to which Wyeth has agreed. We have considered the matter and determined that such an approach is not workable, given that several of the topics, as originally drafted, cover both objectionable and non-objectionable subject matter. It would be unreasonable for Wyeth to produce a witness to cover only some aspects of a given topic only to have to re-produce the same witness to cover additional aspects of that same topic, should the Court rule in Impax's favor with respect to that particular topic.

With respect to Topics 16 and 19 of Impax's Amended Rule 30(b)(6) Notice, as modified by our letter of January 30, 2007, Wyeth proposed that both parties agree not to introduce any evidence at trial on those topics with respect to any underlying activities occurring after June 30, 2006. Later occurring compilation and/or analyses of underlying activities occurring prior to that date can be introduced. You indicated that you would get back to us shortly on this proposal.

Turning to the protective order, it seems clear that both parties would like to resolve this issue prior to Wednesday's status conference. In that vein, and as we mentioned during the telephone conference, we suggest the following language for the protective order with respect to third party designation of material as Highly Confidential after the end of the last sentence of the first paragraph of 3:

> In designating material as Highly Confidential, the non-party must identify any documents previously provided to any of the parties outside of the present Proceeding. Such documents may be disclosed to the in-house counsel listed in Paragraph 9 who are employed by the party previously having access to those documents.

Please let us know whether you find this language acceptable.

As for paragraph 24 of the proposed draft protective order, we noted that we will provide our comments as soon as possible. We hope to get back to you on this tomorrow.

We also discussed today the deficiencies in Impax's document production that we identified in our letters of January 26, 2007, and February 2, 2007. We understand that you are continuing to investigate these matters, and have agreed to apprise us by tomorrow evening of the results of that investigation thus far. We look forward to hearing from you tomorrow on this matter.

You also raised Wyeth's response to Interrogatory No. 35 during our telephone conference. Your February 5th letter stated that Impax objects to Wyeth's counter-proposal regarding Interrogatory No. 35. In today's conference call, Impax withdrew its offer of compromise, and insisted that Wyeth respond to Interrogatory No. 35 as originally drafted, albeit with respect to any time prior to the issuance of the patents in suit. This proposal is unacceptable for the reasons previously set forth in Wyeth's general and specific objections to the interrogatory.

Finally, you raised the question of whether Wyeth intended to offer testimony of a legal expert at trial. As we mentioned during our telephone conference, we are of the view that it is far too premature for Wyeth to determine whether or not it intends to proffer legal expert testimony. You further indicated that you would get back to us

before the status conference as to whether Impax would maintain its objection to the disclosure of Impax confidential information to Dr. Grabowski under the protective order.

Sincerely,

Barbara R. Rudolph

BRR

cc: Mary B. Matterer, Esq. (via facsimile)